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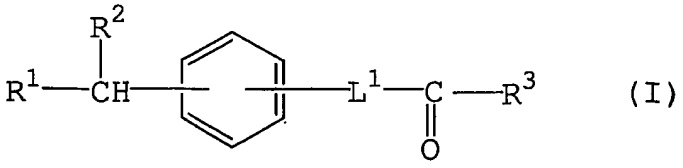
(54) Title: HDAC INHIBITOR



(I)

(57) Abstract: A compound having the following formula (I): wherein R_1 is lower alkyl optionally substituted with one or more suitable substituent(s); aryl optionally substituted with one or more suitable substituent(s); or fused ring, R_2 is acylamino or optionally protected hydroxy, L_1 is lower alkenylene, and R_3 is hydroxyamino, or a salt thereof. The compound is useful as an inhibitor of histone deacetylase.

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DESCRIPTION

HDAC INHIBITOR

TECHNICAL FIELD

The present invention relates to a compound, which is useful as a medicament, and to a pharmaceutical composition comprising the same.

BACKGROUND ART

Histone deacetylase (hereinafter also referred as HDAC) is known to play an essential role in the transcriptional machinery for regulating gene expression, induce histone hyperacetylation and to affect the gene expression. Therefore, it is useful as a therapeutic or prophylactic agent for diseases caused by abnormal gene expression, such as inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections, tumors, etc.

WO 01/38322 discloses an inhibitor of histone deacetylase represented by the following formula:

$$Cy\text{-}L^1\text{-}Ar\text{-}Y^1\text{-}C(O)\text{-}NH\text{-}Z$$

wherein

Cy is cycloalkyl, aryl, heteroaryl or heterocyclyl, each of which is optionally substituted;

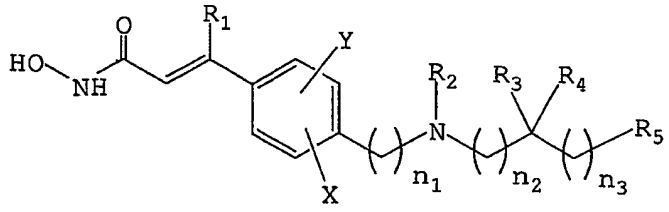
L^1 is $-(CH_2)_m-W-$, wherein m is an integer of 0 to 4, and W is selected from the group consisting of $-C(O)NH-$, $-S(O)_2NH-$, etc.;

Ar is optionally substituted arylene which is optionally fused to an aryl, heteroaryl ring, etc.;

Y^1 is a chemical bond or a straight- or branched-chain saturated alkylene, wherein said alkylene is optionally substituted; and

Z is selected from the group consisting of anilinyl, pyridyl, thiadiazolyl and -O-M, wherein M is H or a pharmaceutically acceptable cation.

WO 0222577 discloses the following hydroxamate compound as a deacetylase inhibitor:



wherein

R_1 is H, halo, or a straight chain C_1-C_6 alkyl;

R_2 is selected from H, C_1-C_{10} alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, C_4-C_9 heterocycloalkylalkyl, cycloalkylalkyl, aryl, heteroaryl, etc.;

R_3 and R_4 are the same or different and independently H, C_1-C_6 alkyl, acyl or acylamino, or R_3 and R_4 together with the carbon to which they are bound to represent C=O, C=S, etc., or R_2 together with the nitrogen to which it is bound and R_3 together with the carbon to which it is bound to form a C_4-C_9 heterocycloalkyl, a heteroaryl, a polyheteroaryl, a non-aromatic polyheterocycle, or a mixed aryl and non-aryl polyheterocycle ring;

R_5 is selected from H, C_1-C_6 alkyl, etc.;

n, n_1, n_2 and n_3 are the same or different and independently selected from 0-6, when n_1 is 1-6, each carbon atom can be optionally and independently substituted with R_3 and/or R_4;

X and Y are the same or different and independently selected from H, halo, C_1-C_4 alkyl, etc.;

or a pharmaceutically acceptable salt thereof.

SUMMARY OF THE INVENTION

The present invention relates to a novel compound, which is useful as a medicament, and to a pharmaceutical composition comprising the same.

More particularly, the present invention relates to a compound, which has a potent inhibitory effect on the activity of histone deacetylase.

The inventors of the present invention have found that a

histone deacetylase inhibitor, such as compound of the formula (I) (hereinafter also referred to as compound [I]), has a potent immunosuppressive effect and potent antitumor effect. Therefore, a histone deacetylase inhibitor such as compound [I] is useful as an active ingredient of an immunosuppressant and an antitumor agent, and useful as a therapeutic or prophylactic agent for diseases such as inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections, tumors, etc.

Accordingly, one object of the present invention is to provide a compound, which has biological activities for treating or preventing the diseases as stated above.

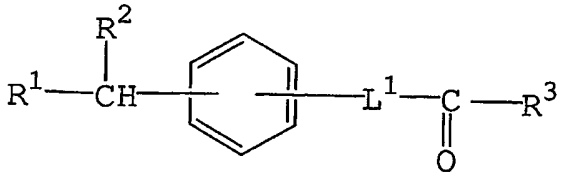
Another object of the present invention is to provide a pharmaceutical composition containing the compound [I] as an active ingredient.

A further object of the present invention is to provide use of the histone deacetylase inhibitors, such as the compound [I], for treating or preventing the diseases as stated above.

A yet further object of the present invention is to provide a commercial package comprising the pharmaceutical composition containing the compound [I] and a written matter associated therewith, the written matter stating that the pharmaceutical composition may or should be used for treating or preventing the diseases as stated above.

Namely, the present invention provides

[1] a compound of the formula (I):



(I)

wherein

R^1 is lower alkyl optionally substituted with one or more suitable substituent(s);

aryl optionally substituted with one or more suitable

substituent(s); or
fused ring,

R^2 is acylamino or optionally protected hydroxy,

L^1 is lower alkenylene, and

R^3 is hydroxyamino,

or a salt thereof;

[2] the compound of the above-mentioned [1], wherein

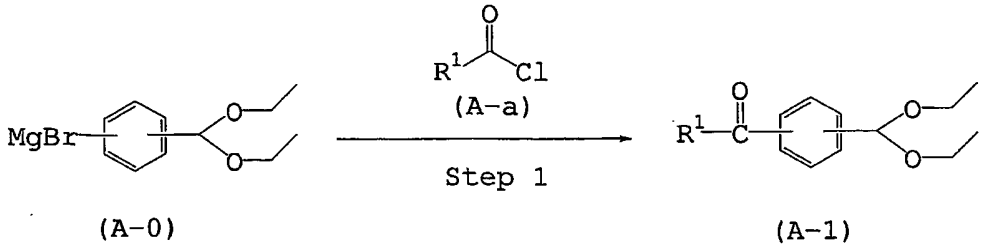
R^1 is lower alkyl optionally substituted with
aryl(lower)alkoxyaryl;
aryl optionally substituted with the group(s) selected from lower alkoxy, halogen, aryl, aryl(lower)alkoxy and mono- or di-substituted amino; or
fused ring, and

R^2 is acylamino selected from lower alkylcarbonylamino, lower alkylsulfonylamino and arylcarbonylamino; or
hydroxy optionally protected with lower alkyl,

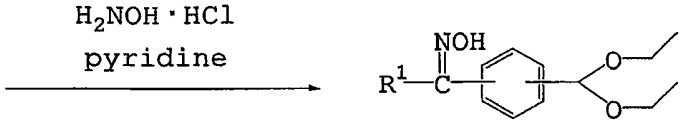
or a salt thereof, etc.

The compound [I] or a salt thereof can be prepared by the process as illustrated in the following reaction schemes.

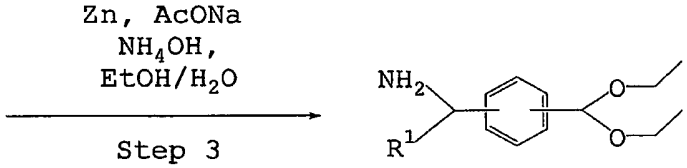
Process A



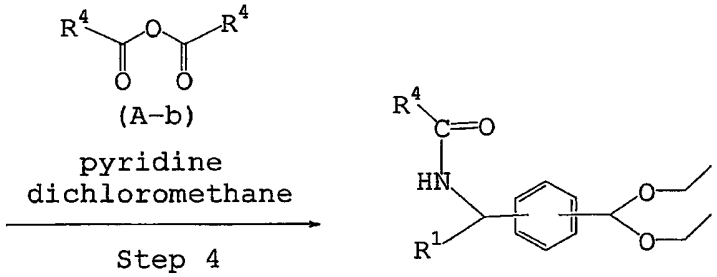
(A-0) (A-1)



(A-2)



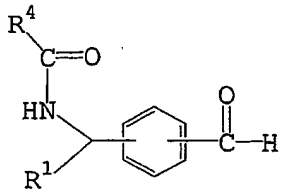
(A-3)



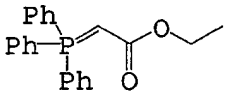
(A-4)

H_2SO_4 5% v/v
THF

Step 5



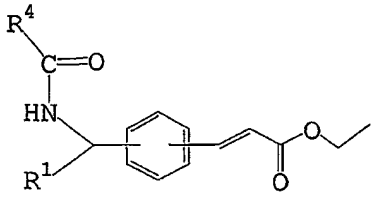
(A-5)



(A-c)

toluene

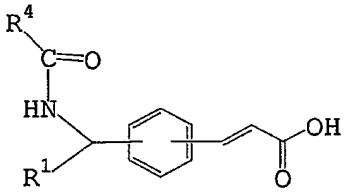
Step 6



(A-6)

1N LiOH
dioxane

Step 7



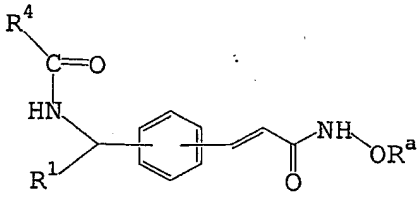
(A-7)

H_2N-OR^a

(A-d)

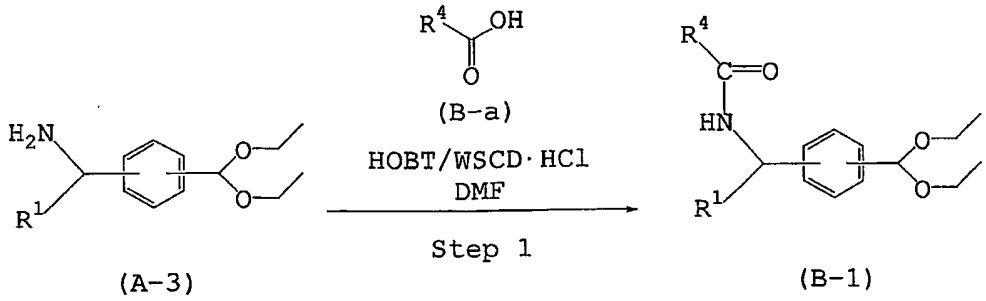
HOBT, WSCD
DMF

Step 8

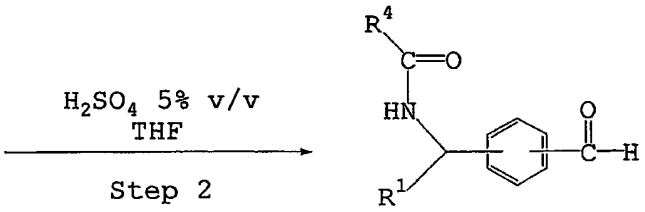


[II-1]

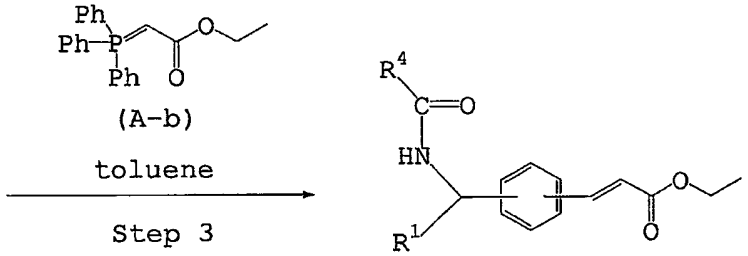
Process B



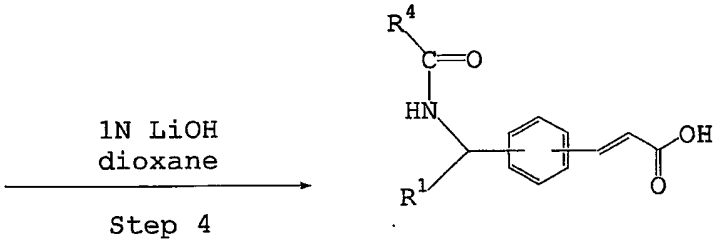
(A-3) (B-1)



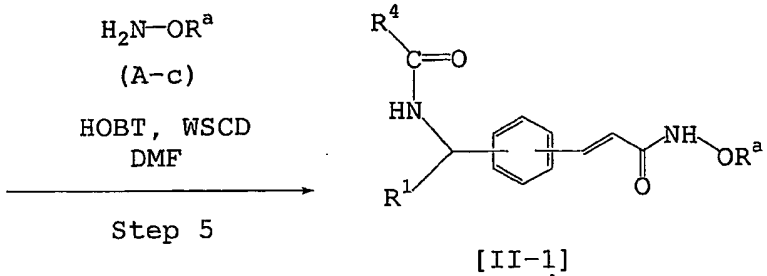
(B-2)



(B-3)

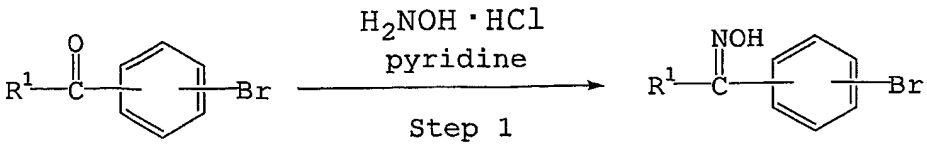


(B-4)

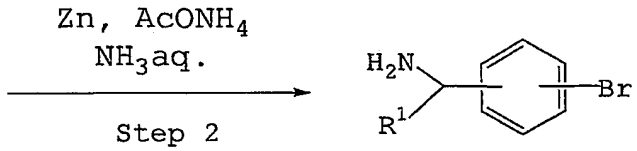


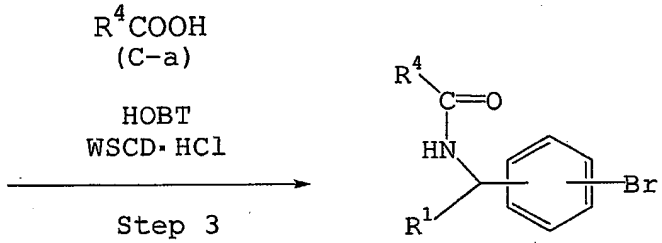
[II-1]

Process C

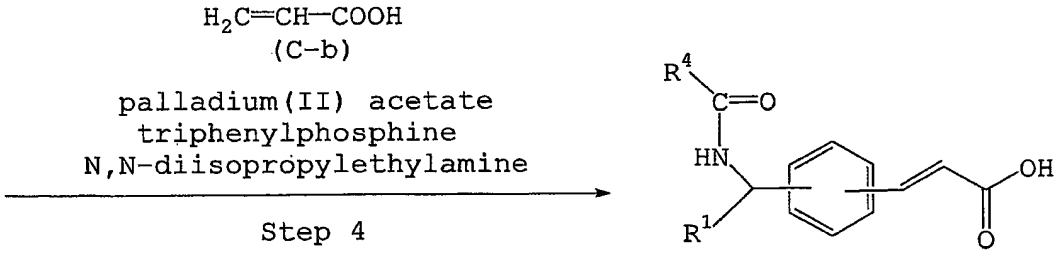


(C-0) (C-1)

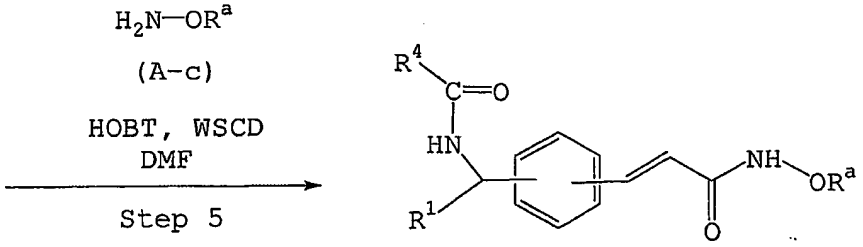




(C-3)

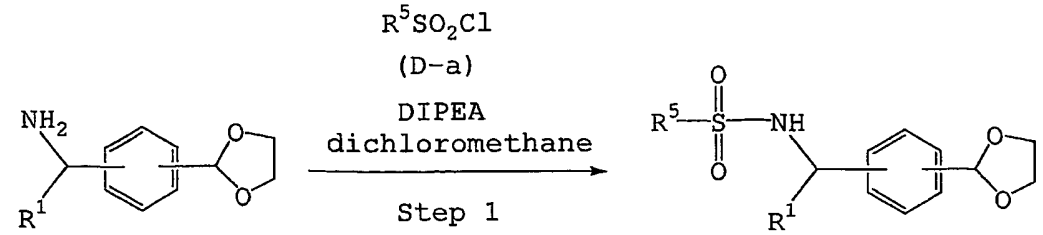


(C-4)

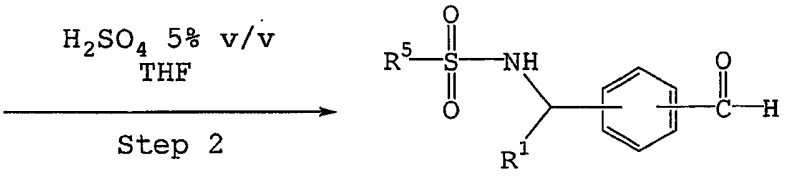


[II-1]

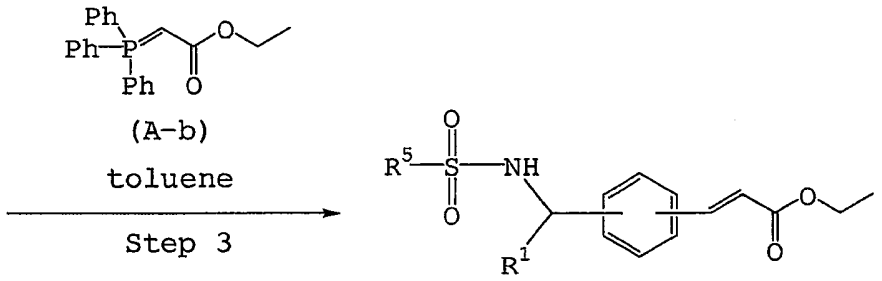
Process D



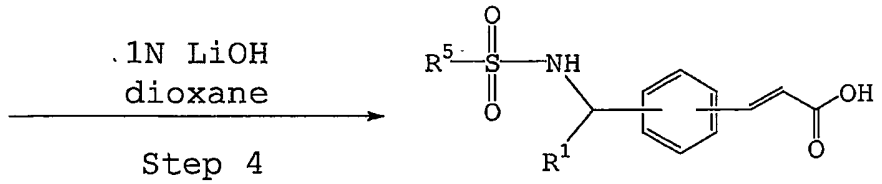
(D-0) (D-1)



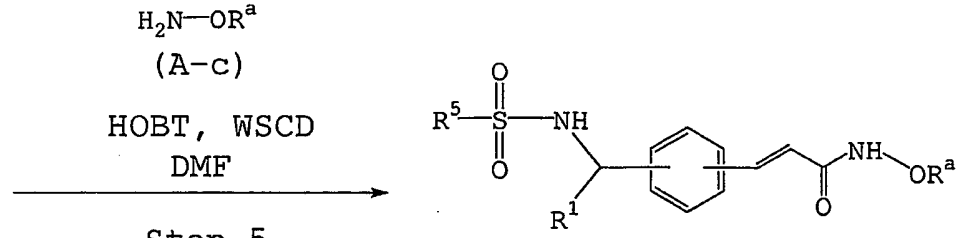
(D-2)



(D-3)

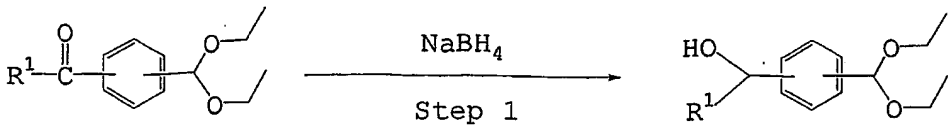


(D-4)



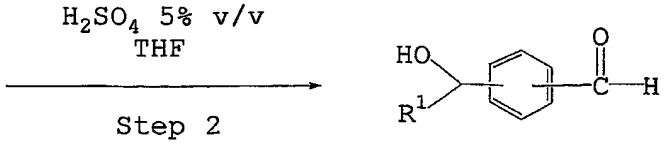
[II-2]

Process E



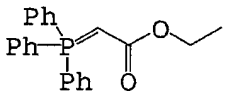
(A-1) (E-1)

Step 1: $NaBH_4$

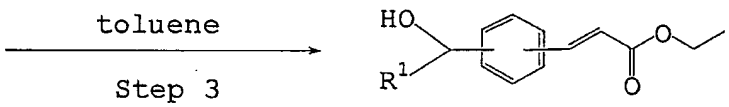


(E-2)

Step 2: H_2SO_4 5% v/v, THF

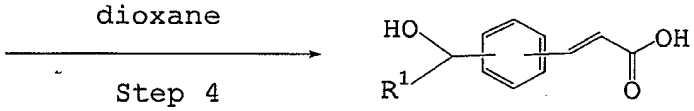


(A-b)



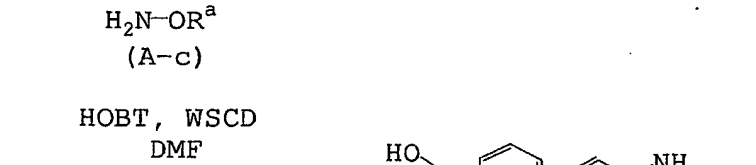
(E-3)

Step 3: toluene



Step 4: 1N LiOH, dioxane

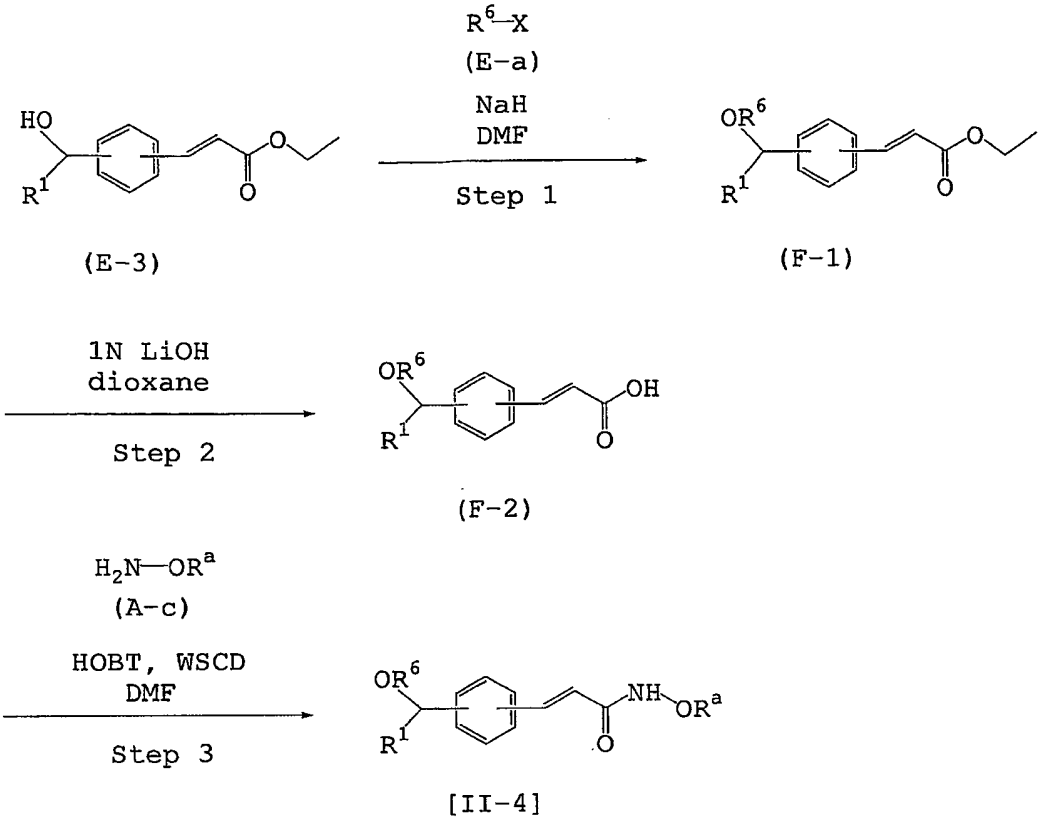
(E-4)



Step 5: H_2N-OR^a (A-c), HOBT, WSCD, DMF

[II-3]

Process F



wherein

R^1 and R^3 are each as defined above,

R^4 is lower alkyl (e.g., methyl, ethyl, etc.) or aryl (e.g., phenyl, etc.),

R^5 is lower alkyl (e.g., methyl, ethyl, etc.), aryl (e.g., phenyl, etc.),

R^6 is hydroxy protecting group (e.g., methyl, etc.),

X is halogen (e.g., iodine, etc.), methanesulfonyloxy, p-toluenesulfonyloxy, etc., and

R^a is hydroxy protecting group (e.g., tetrahydropyranyl, etc.).

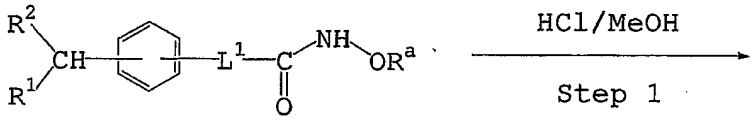
In the above-mentioned Processes A, B, C, D, E and F, the compounds [II-1], [II-2], [II-3] and [II-4] are also encompassed in the scope of the compound [II].

In the above-mentioned Processes A, B, C, D, E and F, each of the starting compounds can be prepared, for example, according to the procedures as illustrated in Preparations in the present

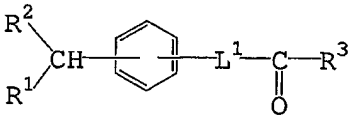
specification or in a manner similar thereto. For example, the compounds (A-1), (A-2), (A-3), (A-4), (A-5), (A-6) and (A-7) can be obtained by the procedures as illustrated in Preparations 1, 2, 3, 4, 5, 6 and 7, respectively; the compounds (B-1), (B-2), (B-3) and (B-4) can be obtained by the procedures as illustrated in Preparations 9, 10, 11 and 12, respectively; the compounds (C-1), (C-2), (C-3) and (C-4) can be obtained by the procedures as illustrated in Preparations 14, 15, 16 and 17, respectively; the compounds (D-1), (D-2), (D-3) and (D-4) can be obtained by the procedures as illustrated in Preparations 34, 35, 36 and 37, respectively; the compounds (E-1), (E-2), (E-3) and (E-4) can be obtained by the procedures as illustrated in Preparations 79, 80, 81 and 82, respectively; and the compounds (F-1) and (F-2) can be obtained by the procedures as illustrated in Preparations 84 and 85, respectively. The compound [II-1] can be obtained by the procedure as illustrated in Preparation 8, 13 or 18, and the compounds [II-2], [II-3] and [II-4] can be obtained by the procedures as illustrated in Preparations 38, 83 and 86, respectively.

The compound [I] of the present invention can be obtained from compound [II] according to the following process.

Preparation of the compound [I]



[II]



[I]

wherein

R^1, R^2, R^3, L^1 and R^a are as defined above.

The Compound [I] is obtained by deprotecting the hydroxy group of the Compound [II].

The reaction may be carried out in the presence of acid, for example, hydrogen chloride solution (e.g., hydrogen chloride in solvent such as methanol, dioxane, ethyl acetate, diethyl ether, etc.), acetic acid, p-toluenesulfonic acid, boric acid, etc.

Optionally, one or more suitable solvent(s) for the deprotection is(are) used. Such solvent includes methanol, ethanol, ethyl acetate, dioxane, diethyl ether, acetic acid, etc.

The temperature of the reaction is not critical and the reaction is usually carried out under from cooling to heating.

This process is exemplified by Example 1, etc.

When the compound [I] has stereoisomers, such isomers are also encompassed in the present invention.

The compound [I] may form a salt, which is also encompassed in the present invention. For example, when a basic group such as an amino group is present in a molecule, the salt is exemplified by an acid addition salt (e.g., salt with an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid,, etc., salt with an organic acid such as methanesulfonic acid, fumaric acid, maleic acid, mandelic acid, citric acid, salicylic acid, etc.), and when an acidic group such as carboxyl group is present, the salt is exemplified by a basic salt (e.g., salt with a metal such as sodium, potassium, calcium, magnesium, aluminum, etc., salt with an amino acid such as lysine, etc.), etc.

In addition, solvates of the compound [I] such as hydrate, ethanolate, etc., are also encompassed in the present invention.

Suitable examples and illustration of the various definitions in the above and subsequent descriptions, which the present invention intends to include within its scope, are explained in detail as follows:

The term "halogen" includes fluorine, chlorine, bromine, and iodine.

The term "lower" used in the description is intended to mean 1 to 6 carbon atoms, unless otherwise indicated.

Suitable example of "one or more" means the number of 1 to 6, preferably 1 to 3.

Suitable examples of the "lower alkyl" include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl, neopentyl, hexyl, isohexyl, etc. Suitable lower alkyl for the "lower alkyl optionally substituted with one or more suitable substituent(s)" for R^1 includes methyl, etc.

Suitable examples of the "lower alkoxy" include straight or branched one having 1 to 6 carbon atom(s), such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, tert-pentyloxy, neopentyloxy, hexyloxy, isohexyloxy, etc.

Suitable examples of the "aryl" include a C_6-C_{16} aryl such as phenyl, naphthyl, anthryl, pyrenyl, phenanthryl, azulenyl, etc. Suitable examples of the "aryl" for the "aryl optionally substituted with one or more suitable substituent(s)" for R^1 include phenyl, etc.

Suitable examples of the "fused ring" include a 5- or 6-membered fused ring, each of which may contain one or more heteroatom selected from a sulfur atom, an oxygen atom and a nitrogen atom besides carbon atoms and one or more carbon atom(s) is/are optionally replaced with oxo group(s). Suitable examples of the "fused ring" include indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, quinoxalinyl, imidazopyridyl (e.g., imidazo[4,5-c]pyridyl, etc.), tetrahydroimidazopyridyl (e.g., 4,5,6,7-tetrahydro[4,5-c]pyridyl, etc.), 7-azabicyclo[2.2.1]heptyl, 3-azabicyclo[3.2.2]nonanyl, benzoxazolyl, benzodioxolyl, benzoxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzothienyl, benzodithiinyl, benzoxathiinyl, etc. Suitable examples of the "fused ring" for R^1 include 1,3-benzodioxol-5-yl, etc.

Suitable examples of the "acyl" for the "acylamino" include

alkanoyl [e.g., formyl, lower alkyl-carbonyl (e.g., acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, pivaloyl, 2,2-dimethylpropanoyl, hexanoyl, etc.), heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.];

alkoxycarbonyl [e.g., lower alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, etc.), etc.];

lower alkyl-carbonyloxy(lower)alkylcarbonyl (e.g., acetyloxyacetyl, ethylcarbonyloxyacetyl, etc.);

arylcarbonyl [e.g., C_{6-10} arylcarbonyl (e.g., benzoyl, toluoyl, naphthoyl, fluorenylcarbonyl, etc.)];

arylalkanoyl [e.g., phenyl(lower)alkanoyl (e.g., phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(lower)alkanoyl (e.g., naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc.), etc.];

arylalkenoyl [e.g., aryl(C_3-C_6)alkenoyl (e.g., phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl, etc.), etc.)];

naphthylalkenoyl [e.g., naphthyl(C_3-C_6)alkenoyl (e.g., naphthylpropenoyl, naphthylbutenoyl, naphthylmethacryloyl, naphthylpentenoyl, naphthylhexenoyl, etc.), etc.];

arylalkoxycarbonyl [e.g., aryl(lower)alkoxycarbonyl such as phenyl(lower)alkoxycarbonyl (e.g., benzyloxycarbonyl, etc.), fluorenyl(lower)alkoxycarbonyl (e.g., fluorenylmethyloxycarbonyl, etc.), etc.];

aryloxycarbonyl (e.g., phenoxycarbonyl, naphthyloxycarbonyl, etc.);

aryloxyalkanoyl [e.g., aryloxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, etc.), etc.];

heterocyclic acyl (e.g., heterocycliccarbonyl, etc.);

heterocyclic alkanoyl [e.g., heterocyclic(lower)alkanoyl (e.g.,

heterocyclic acetyl, heterocyclic propanoyl, heterocyclic butanoyl, heterocyclic pentanoyl, heterocyclic hexanoyl, etc.), etc.]; heterocyclic alkenoyl [e.g., heterocyclic(lower)alkenoyl (e.g., heterocyclic propenoyl, heterocyclic butenoyl, heterocyclic pentenoyl, heterocyclic hexenoyl, etc.)];
carbamoyl;
alkylcarbamoyl [e.g., lower alkylcarbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.)];
alkoxycarbamoyl [e.g., lower alkoxycarbamoyl (e.g., methoxycarbamoyl, ethoxycarbamoyl, etc.)], etc.;
arylcarbamoyl [e.g., C_{6-10} arylcarbamoyl (e.g., phenylcarbamoyl, naphthylcarbamoyl, etc.), etc.];
arylthiocarbamoyl [e.g., C_{6-10} arylthiocarbamoyl (e.g., phenylthiocarbamoyl, naphthylthiocarbamoyl, etc.), etc.];
alkylsulfonyl [e.g., lower alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.)];
alkoxysulfonyl [e.g., lower alkoxysulfonyl (e.g., methoxysulfonyl, ethoxysulfonyl, etc.)], etc.;
arylsulfonyl (e.g., phenylsulfonyl, etc.);
arylglyoxyloyl [e.g., C_{6-10} arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl, etc.), etc.];
heterocyclicglyoxyloyl, etc. Each of the acyl is optionally substituted by one or more suitable substituent(s).

Suitable examples of hydroxy protective group for the "optionally protected hydroxy" for R^2 include
lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, etc.);
lower alkoxy(lower)alkyl (e.g., methoxymethyl, etc.);
lower alkoxy(lower)alkoxy(lower)alkyl (e.g., 2-methoxyethoxymethyl, etc.);
aryl(lower)alkyl in which the aryl portion is optionally substituted with one or more suitable substituent(s) (e.g., benzyl (Bn), p-methoxybenzyl, 2,3-dimethoxybenzyl, etc.);
aryl(lower)alkoxy(lower)alkyl in which the aryl portion is optionally substituted with one or more suitable substituent(s)

(e.g., benzyloxymethyl, p-methoxybenzyloxymethyl, etc.);
lower alkylthio(lower)alkyl (e.g., methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl, etc.);
heterocyclic group (e.g., tetrahydropyranyl, etc.);
trisubstituted silyl [e.g., tri(lower)alkylsilyl (e.g., trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyldimethylsilyl (TBDMS), tri-tert-butylsilyl, etc.), lower alkyldiarylsilyl (e.g., methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenylsilyl (TBDPS), etc.), etc.];
acyl as described above;
lower alkenyl (e.g., vinyl, allyl, etc.), etc.

Suitable examples of the "lower alkenylene" include a straight or branched alkenylene having 1 to 6 carbon atom(s), such as vinylene, 1-methylvinylene, 2-methylvinylene, 1-propenylene, 2-propenylene, 2-methyl-1-propenylene, 2-methyl-2-propenylene, 1-butenylene, 2-butenylene, 3-butenylene, 1-pentenylene, 2-pentenylene, 3-pentenylene, 4-pentenylene, 1-hexenylene, 2-hexenylene, 3-hexenylene, 4-hexenylene, 5-hexenylene, etc. Suitable examples of the "lower alkenylene" for L^1 include vinylene, etc.

Suitable examples of R^1 for the compound [I] include lower alkyl optionally substituted with aryl(lower)alkoxyaryl (e.g., 4-benzyloxyphenyl, etc.), of which the preferred are methyl, (4-benzyloxyphenyl)methyl, etc.;
aryl optionally substituted with the group(s) selected from lower alkoxy (e.g., methoxy, ethoxy, propoxy, etc.), halogen (e.g., chloro, bromo, iodo, etc.), aryl (e.g., phenyl, naphthyl, etc.), aryl(lower)alkoxy (e.g., benzyloxy, naphthylmethyloxy, etc.) and mono- or di-substituted amino (e.g., methylamino, ethylamino, N,N-dimethylamino, etc.), of which the preferred are chlorophenyl, ethoxyphenyl, benzyloxyphenyl, biphenylyl, N,N-dimethylaminophenyl, etc.; and
fused ring (e.g., benzodioxolyl, etc.), of which the preferred

are 1,3-benzodioxol-5-yl, etc., etc.

Suitable examples of "acylamino" for R^2 include lower alkyl-carbonylamino (e.g., acetylamino, ethylcarbonylamino, propylcarbonylamino, etc.), lower alkylsulfonylamino (e.g., methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino, etc.), arylcarbonylamino (e.g., phenylcarbonylamino, naphthylcarbonylamino, etc.), etc., of which the preferred are acetylamino, methylsulfonylamino, phenylcarbonylamino, etc.

Suitable examples of "optionally protected hydroxy" include hydroxy, lower alkoxy (e.g., methoxy, ethoxy, propoxy, etc.), of which the preferred are hydroxy, methoxy, etc.

The following abbreviations are also used in the present specification: Boc (t-butyloxycarbonyl); HOBT (1-hydroxybenzotriazole); WSCD (1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide); DMF (N,N-dimethylformamide); aq. (aqueous solution); Me (methyl); MeOH (methanol); Et (ethyl); EtOH (ethanol); tBu (t-butyl); t-Boc (t-butoxycarbonyl); TsCl (p-toluenesulfonyl chloride); Ac (acetyl); AcOH (acetic acid); Ph (phenyl); DIEA (diisopropylethylamine); Bn (benzyl); Bz (benzoyl); TBAI (tetrabutylammonium iodide); TBAF (tetrabutylammonium fluoride); CAN (cerium ammonium nitrate); THP (tetrahydropyranyl); IPE (diisopropylether).

Test Method

In order to show the usefulness of the compound [I] of the invention, the pharmacological test result of the representative compound of the present invention is shown in the following.

Test 1: Determination of histone deacetylase inhibitory activity

The partial purification of human histone deacetylase, the preparation of [^{3}H] acetyl histones, and the assay for histone deacetylase activity were performed as follows basically according to the method as proposed by Yoshida et al.

Partial purification of human histone deacetylase

The human histone deacetylase was partially purified from human T cell leukemia Jurkat cells. Jurkat cells (5×10^8 cells) were suspended in 40 mL of the HDA buffer consisting of 15 mM

potassium phosphate (pH 7.5), 5% glycerol and 0.2 mM EDTA. After homogenization, nuclei were collected by centrifugation (35,000 × g, 10 min) and homogenized in 20 mL of the same buffer supplemented with 1 M $(NH_4)_2SO_4$. The viscous homogenate was sonicated and clarified by centrifugation (35,000 × g, 10 min), and the deacetylase was precipitated by raising the concentration of $(NH_4)_2SO_4$ to 3.5 M. The precipitated protein was dissolved in 10 mL of the HDA buffer and dialyzed against 4 liters of the same buffer. The dialyzate was then loaded onto a DEAE-cellulose (Whatman DE52) column (25 × 85 mm) equilibrated with the same buffer and eluted with 300 mL of a linear gradient (0-0.6 M) of NaCl. A single peak of histone deacetylase activity appeared between 0.3 and 0.4 M NaCl.

Preparation of [^{3}H] acetyl histone

To obtain [^{3}H] acetyl-labeled histone as the substrate for the histone deacetylase assay, 1 x 10^8 cells of Jurkat in 20 mL of RPMI-1640 medium (supplemented with 10% FBS, penicillin (50 units/mL) and streptomycin (50 μg/mL)) were incubated with 300 MBq [^{3}H] sodium acetate in the presence of 5 mM sodium butyrate for 30 min in 5% CO_2-95% air atmosphere at 37°C in a 75 cm^2 flask, harvested into a centrifuge tube (50 mL), collected by centrifugation at 1000 rpm for 10 min, and washed once with phosphate-buffered saline. The washed cells were suspended in 15 mL of ice-cold lysis buffer (pH 6.5, 10 mM Tris-HCl, 50 mM sodium bisulfite, 1% Triton X-100, 10 mM $MgCl_2$, 8.6% sucrose). After Dounce homogenization (30 stroke), the nuclei were collected by centrifugation at 1000 rpm for 10 min, washed 3 times with 15 mL of the lysis buffer, and once with 15 mL of ice-cooled washing buffer (pH 7.4, 10 mM Tris-HCl, 13 mM EDTA) successively. The pellet was suspended in 6 mL of ice-cooled water using a mixer, and 68 μl of H_2SO_4 was added to the suspension to give a concentration of 0.4 N. After incubation at 4°C for 1 hr, the suspension was centrifuged for 5 min at 15,000 rpm, and the supernatant was taken and mixed with 60 mL of acetone. After overnight incubation at -20°C, the coagulated material was

collected by microcentrifugation, air-dried, and stored at -80°C.

Assay for histone deacetylase activity

For the standard assay, 10 µl of [^{3}H] acetyl-labeled histones were added to 90 µl of the enzyme fraction, and the mixture was incubated at 25°C for 30 min. The reaction was stopped by addition of 10 µl of HCl. The released [^{3}H] acetic acid was extracted with 1 mL of ethyl acetate, and 0.9 mL of the solvent layer was taken into 10 mL of toluene scintillation solution for determination of radioactivity.

Test 2: Determination of T-cell growth inhibitor activity

The T lymphocyte blastogenesis test was performed in microtiter plates with each well containing 1.5 × 10^5 splenic cells of Lewis rats in 0.1 mL RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS), 50 mM 2-mercaptoethanol, penicilln (100 units/mL) and streptomycin (100 µg/mL), to which Concanavalin A (1 µg/mL) was added. The cells were incubated at 37°C in a humidified atmosphere of 5% CO_2 for 72 hrs. After the culture period, suppressive activities of the test compounds in T lymphocyte blastogenesis were quantified by AlamarBlue (trademark) Assay. The test samples were dissolved in DMSO and further diluted with RPMI-1640 medium and added to the culture. The activities of the test compounds were expressed as IC_{50}.

The results of those tests are shown in the Table 1.

Table 1: HDAC inhibitory activity and T-cell growth inhibitory activity of the compound of the present invention

Examples	Test 1: HDAC inhibitory activity IC_{50} (nM)	Test 2: T-cell growth inhibitory activity IC_{50} (nM)
Compound 2	<200	<2000
Compound 10	<200	<2000
Compound 13	<200	<2000
Compound 14	<200	<2000

The pharmaceutical composition of the present invention comprising histone deacetylase inhibitor such as the compound [I] is useful as a therapeutic or prophylactic agent for diseases caused by abnormal gene expression, such as inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), protozoal infection, etc. Further, it is useful as an antitumor agent or immunosuppressant, which prevents an organ transplant rejection and autoimmune diseases as exemplified below.

Rejection reactions by transplantation of organs or tissues (e.g., heart, kidney, liver, bone marrow, skin, cornea, lung, pancreas, small intestine, limb, muscle, nerve, intervertebral disc, trachea, myoblast, cartilage, etc.), etc.;
graft-versus-host reactions following bone marrow transplantation;
autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, etc.);
infections caused by pathogenic microorganisms (e.g., Aspergillus fumigatus, Fusarium oxysporum, Trichophyton asteroides, etc.), etc.

Furthermore, pharmaceutical preparations of the histone

deacetylase inhibitor, such as the compound [I], are useful for the therapy or prophylaxis of the following diseases.

Inflammatory or hyperproliferative skin diseases or cutaneous manifestations of immunologically-mediated diseases (e.g., psoriasis, atopic dermatitis, contact dermatitis, eczematoid dermatitis, seborrheic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, erythema, dermal eosinophilia, lupus erythematosus, acne, alopecia areata, etc.);

autoimmune diseases of eye (e.g., keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical keratitis, corneal epithelial dystrophy, keratoleukoma, ocular premphigus, Mooren's ulcer, scleritis, Grave's ophthalmopathy, Vogt-Koyanagi-Harada syndrome, keratoconjunctivitis sicca (dry eye), phlyctenule, iridocyclitis, sarcoidosis, endocrine ophthalmopathy, etc.);

reversible obstructive airway diseases [e.g., asthma (e.g., bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, and dust asthma), particularly chronic or inveterate asthma (e.g., late asthma, airway hyper-responsiveness, etc.), bronchitis, etc.];

mucosal or vascular inflammations (e.g., gastric ulcer, ischemic or thrombotic vascular injury, ischemic bowel diseases, enteritis, necrotizing enterocolitis, intestinal damages associated with thermal burns, leukotriene B4-mediated diseases, etc.);

intestinal inflammations/allergies (e.g., coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, etc.);

food-related allergic diseases with symptomatic manifestation remote from the gastrointestinal tract (e.g., migrain, rhinitis, eczema, etc.);

renal diseases (e.g., intestitial nephritis, Goodpasture's syndrome, hemolytic uremic syndrome, diabetic nephropathy, etc.);

nervous diseases (e.g., multiple myositis, Guillain-Barre syndrome, Meniere's disease, multiple neuritis, solitary neuritis,

cerebral infarction, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), radiculopathy, etc.);
cerebral ischemic diseases [e.g., head injury, hemorrhage in brain (e.g., subarachnoid hemorrhage, intracerebral hemorrhage, etc.), cerebral thrombosis, cerebral embolism, cardiac arrest, stroke, transient ischemic attack (TIA), hypertensive encephalopathy, etc.];
endocrine diseases (e.g., hyperthyroidism, Basedow's disease, etc.);
hematic diseases (e.g., pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, anerythroplasia, etc.);
bone diseases (e.g., osteoporosis, etc.);
respiratory diseases (e.g., sarcoidosis, pulmonary fibrosis, idiopathic interstitial pneumonia, etc.);
skin diseases (e.g., dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photosensitivity, cutaneous T-cell lymphoma, etc.);
circulatory diseases (e.g., arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocardosis, etc.);
collagen diseases (e.g., scleroderma, Wegener's granuloma, Sjögren's syndrome, etc.);
adiposis;
eosinophilic fasciitis;
periodontal diseases (e.g., damage to gingiva, periodontium, alveolar bone or substantia ossea dentis, etc.);
nephrotic syndrome (e.g., glomerulonephritis, etc.);
male pattern alopecia, alopecia senile;
muscular dystrophy;
pyoderma and Sezary syndrome;
chromosome abnormality-associated diseases (e.g., Down's syndrome, etc.);
Addison's disease;
active oxygen-mediated diseases (e.g., organ injury [e.g.,

ischemic circulation disorders of organs (e.g., heart, liver, kidney, digestive tract, etc.) associated with preservation and transplantation, etc.], ischemic diseases (e.g., thrombosis, cardial infarction, etc.), intestinal diseases (e.g., endotoxin shock, pseudomembranous colitis, drug- or radiation-induced colitis, etc.), renal diseases (e.g., ischemic acute renal insufficiency, chronic renal failure, etc.), pulmonary diseases [e.g., toxicosis caused by pulmonary oxygen or drugs (e.g., paracort, bleomycin, etc.), lung cancer, pulmonary emphysema, etc.], ocular diseases (e.g., cataracta, iron-storage disease (siderosis bulbi), retinitis, pigmentosa, senile plaques, vitreous scarring, corneal alkali burn, etc.), dermatitis (e.g., erythema multiforme, linear immunoglobulin A bullous dermatitis, cement dermatitis, etc.), other diseases [e.g., gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution (e.g., air pollution, etc.), aging, carcinogen, metastasis of carcinoma, hypobaropathy, etc.], etc.};
diseases caused by histamine release or leukotriene C4 release;
restenosis of coronary artery following angioplasty and prevention of postsurgical adhesions;
autoimmune diseases and inflammatory conditions [e.g., primary mucosal edema, autoimmune atrophic gastritis, premature menopause, male sterility, juvenile diabetes mellitus, pemphigus vulgaris, pemphigoid, sympathetic ophthalmitis, lens-induced uveitis, idiopathic leukopenia, active chronic hepatitis, idiopathic cirrhosis, discoid lupus erythematosus, autoimmune orchitis, arthritis (e.g., arthritis deformans, etc.), polychondritis, etc.];
Human Immunodeficiency Virus (HIV) infection, AIDS;
allergic conjunctivitis;
hypertrophic cicatrix and keloid due to trauma, burn, surgery, etc., etc.

Therefore, the pharmaceutical composition of the present invention is useful for the therapy and prophylaxis of liver diseases [e.g., immunogenic diseases (e.g., chronic autoimmune

liver diseases such as autoimmune hepatic diseases, primary biliary cirrhosis, sclerosing cholangitis, etc.), partial liver resection, acute liver necrosis (e.g., necrosis caused by toxins, viral hepatitis, shock or anoxia, etc.), hepatitis B, non-A non-B hepatitis, hepatocirrhosis, hepatic failure (e.g., fulminant hepatitis, late-onset hepatitis and "acute-on-chronic" liver failure (acute liver failure on chronic liver diseases), etc.), etc.].

The pharmaceutical composition of the present invention can be used in the form of pharmaceutical preparation, for example, in a solid, semisolid or liquid form, which contains the histone deacetylase inhibitor, such as the compound [I], as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral administrations. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, injections, ointments, liniments, eye drops, lotion, gel, cream, and any other form suitable for use.

The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in a solid, semisolid, or liquid form. Additionally, auxiliary, stabilizing, thickening, solubilizing and coloring agents and perfumes may be used in combination with the carrier.

For application to human, the composition is preferably applied by intravenous, intramuscular, topical or oral administration, or by a vascular stent impregnated with the compound [I]. While the dosage of therapeutically effective amount of the histone deacetylase inhibitor, such as the compound [I], varies depending upon the age and condition of each individual patient to be treated, when an individual patient is to be treated, in the case of intravenous administration, a daily

dose of 0.01-10 mg of the histone deacetylase inhibitor, such as the compound [I], per kg weight of human being, in the case of intramuscular administration, a daily dose of 0.1-10 mg of the histone deacetylase inhibitor, such as the compound of the formula [I], per kg body weight of human being, and in the case of oral administration, a daily dose of 0.5-50 mg of the histone deacetylase inhibitor, such as the compound [I], per kg body weight of human being, is generally given for treatment.

During the preparation of the above-mentioned pharmaceutical administration forms, the compound [I] or a salt thereof can be also combined together with other immunosuppressive substances, such as repamycin, mycophenolic acid, cyclosporin A, tacrolimus and brequinar sodium.

Hereinafter the reactions in respective Preparations and Examples for preparing the compound [I] of the present invention are explained in more detail. The invention should not be restricted by the following Preparations and Examples in any way.

Preparation 1

To magnesium turning (985 mg) was dropwisely added a solution of 4-bromobenzaldehyde diethyl acetal (10 g) in tetrahydrofuran (100 mL) under nitrogen atmosphere. The reaction mixture was stirred at ambient temperature until the magnesium disappeared (for 1 hr). The resulting Grignard's reagent was added dropwise at 0°C to a mixture of 4-(dimethylamino)benzoyl chloride (7.08 g) and bis(triphenylphosphine)nickel(II) chloride (75.7 mg) in tetrahydrofuran (100 mL) with stirring, and the mixture was allowed to warm to ambient temperature and stirred for 2 hrs. Saturated aqueous ammonium chloride solution was added to the reaction mixture, and the mixture was stirred for 30 min. The reaction mixture was extracted with ethyl acetate, and the organic phase was washed sequentially with saturated aqueous ammonium chloride solution, saturated aqueous sodium hydrogen carbonate solution and brine. The organic phase was dried over sodium sulfate, and the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography (eluting

with chloroform and methanol (95:5)) to give Compound (1) as brown oil (10.5 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.26 (6H, t, J=7.4 Hz), 3.08 (6H, s), 3.61 (4H, m), 5.57 (1H, s), 6.68 (2H, d, J=8.1 Hz), 7.56 (2H, d, J=8.4 Hz), 7.72 (2H, d, J=8.1 Hz), 7.89 (2H, d, J=8.4 Hz).

Preparation 2

To a stirred solution of Compound (1) (10.5 g) in ethanol (80 mL) were added hydroxylamine hydrochloride (8.91 g) and pyridine (77.8 mL). The reaction mixture was stirred at ambient temperature for 14 hrs, followed by addition of hydroxylamine hydrochloride (8.91 g) and additional stirring for 3 hrs. The reaction mixture was poured into 300 mL of saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with saturated aqueous ammonium chloride solution and brine, and dried over sodium sulfate. The solvent was removed in vacuo, and the residue was purified by silica gel colomn chromatography (eluting with chloroform and methanol (95:5)). The resulting solid was triturated with diisopropyl ether:hexane = 1:1 to give Compound (2) as a pale yellow powder (4.89 g). The (E) and (Z) mixture was used in the next reaction.

Preparation 3

To a suspension of Compound (2) (4.89 g), zinc powder (4.67 g) and ammonium acetate (1.1 g) in ethanol (50 mL) was added aqueous ammonia (28%, 38.2 mL), and the mixture was refluxed for 1 hr. The resulting zinc was filtered off and the organic solvent was removed in vacuo. The residue was extracted with ethyl acetate. The organic phase was sequentially washed with saturated aqueous sodium hydrogen carbonate solution, water, and brine, and dried over sodium sulfate. The solvent was removed in vacuo to give Compound (3) as yellow oil (4.57 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.22 (6H, t, J=7.0 Hz), 2.91 (6H, s), 3.52 (2H, m), 3.60 (2H, m), 5.14 (1H, s), 5.46 (1H, s), 6.68 (2H, d, J=8.7 Hz), 7.20 (2H, d, J=9.1 Hz), 7.36 (2H, d, J=8.4 Hz), 7.40 (2H, d, J=8.4 Hz);

MASS (ES+): m/e 312 ($M-NH_2$).

Preparation 4

To a stirred solution of Compound (3) (2.6 g) in dichloromethane (25 mL) were added acetic anhydride (0.822 mL) and pyridine (0.704 mL). The reaction mixture was stirred at ambient temperature for 3 hrs. The solvent was removed in vacuo. The residue was extracted with ethyl acetate and washed with saturated ammonium chloride solution, saturated sodium hydrogen carbonate solution and brine. The organic phase was dried over sodium sulfate, and the solvent was removed in vacuo. The resulting yellow oil was purified by silica gel column chromatography eluted with chloroform: methanol=95: 5 to give Compound (4) as yellow oil (2.48 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.23 (6H, t, J=7.2 Hz), 2.05 (3H, s), 2.93 (6H, s), 3.53 (2H, m), 3.61 (2H, m), 5.47 (1H, s), 5.95 (1H, d, J=7.2 Hz), 6.16 (1H, d, J=7.2 Hz), 6.66 (2H, d, J=8.4 Hz), 7.06 (2H, d, J=8.8 Hz), 7.23 (2H, d, J=8.1 Hz), 7.41 (2H, d, J=8.0 Hz);

MASS (ES+): m/e 371 (M+1).

Preparation 5

To a solution of Compound (4) (2.48 g) in tetrahydrofuran (25 mL) was added 5% v/v sulfuric acid (10 mL), and the mixture was stirred for 30 min. The pH value of the mixture was adjusted to 8 with 1N sodium hydroxide. The mixture was extracted with ethyl acetate, and the organic phase was washed with saturated aqueous sodium hydrogen carbonate solution, water and brine, and dried over sodium sulfate. The solvent was removed in vacuo, and the residue was triturated with diisopropyl ether to give Compound (5) as a pale yellow powder (1.66 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.09 (3H, s), 2.95 (3H, s), 6.00 (1H, d, J=7.0 Hz), 6.18 (1H, d, J=7.3 Hz), 6.68 (2H, d, J=8.8 Hz), 7.05 (2H, d, J=8.5 Hz), 7.44 (2H, d, J=8.0 Hz), 7.85 (2H, d, J=7.6 Hz), 10.0 (1H, s);

MASS (ES+): m/e 297 (M+1).

Preparation 6

To a suspension of Compound (5) (1.6 g) in toluene (16 mL) was added ethyl (triphenylphosphoranylidene)acetate (2.07 g), and the mixture was heated at 70°C for 30 min. Additional ethyl (triphenylphosphoranylidene)acetate (690 mg) was added thereto, and the mixture was heated for 30 min. The solvent was removed in vacuo to give Compound (6), which was used in the next reaction without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.34 (3H, t, J=7.1 Hz), 2.07 (3H, s), 2.94 (6H, s), 4.26 (2H, q, J=7.1 Hz), 5.98 (1H, d, J=7.6 Hz), 6.14 (1H, d, J=16.2 Hz), 6.67 (1H, d, J=8.8 Hz), 7.06 (1H, d, J=8.4 Hz);

MASS (ES+): m/e 367 (M+1).

Preparation 7

To a solution of Compound (6) (1.98 g, as a mixture with triphenylphosphine oxide) in dioxane (20 mL) was added 1N lithium hydroxide (21.6 mL), and the mixture was stirred at ambient temperature for 14 hrs. The mixture was acidified with 1N hydrochloric acid to pH 4 and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and the solvent was removed in vacuo. The resulting brown form was triturated with diisopropyl ether to give Compound (7) as a colorless powder (1.73 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.06 (3H, s), 2.93 (6H, s), 6.12 (1H, m), 6.9 (1H, d, J=16.0 Hz), 6.49 (1H, br), 6.68 (2H, d, J=8.7 Hz), 7.05 (2H, d, J=8.8 Hz), 7.27 (2H, d, J=8.0 Hz), 7.48 (2H, d, J=8.4 Hz), 7.67 (1H, d, J=16.0 Hz):

MASS (ES+): m/e 339 (M+1).

Preparation 8

To a stirred solution of Compound (7) (1.73 g) in N,N-dimethylformamide (17 mL) were added 1-hydroxybenzotriazole (HOBT, 898 mg), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (WSCD, 1.03 g) and O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (659 mg), and the mixture was stirred for 90 min. Additional HOBT (499 mg), WSCD (502 mg) and O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (330

mg) were added thereto, and the mixture was stirred for 30 min. The mixture was poured into water and extracted with ethyl acetate. The organic phase was sequentially washed with saturated aqueous ammonium chloride solution, sodium hydrogen carbonate solution and brine. The organic phase was dried over sodium sulfate and concentrated in vacuo. The resulting pale yellow form was triturated with diisopropyl ether to give Compound (8) as a pale yellow powder (2.09 g). The obtained Compound (8) was used in Example 1.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.63 (3H, br), 1.85 (3H, br), 2.06 (3H, s), 2.93 (6H, s), 3.65 (1H, br), 3.97 (1H, br), 5.01 (1H, br), 6.06 (1H, d, J=7.7 Hz), 6.13 (1H, d, J=7.4 Hz), 6.67 (2H, d, J=8.8 Hz), 6.85 (1H, br), 7.05 (2H, d, J=8.9 Hz), 7.24 (2H, d, J=8.0 Hz), 7.44 (2H, d, J=7.7 Hz), 7.67 (1H, br.d, J=15.9 Hz);
MASS (ES+): m/e 438 (M+1).

Preparation 9

To a stirred solution of Compound (3) (2 g) in N,N-dimethylformamide were added HOBT (1.07 g), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSCD-HCl, 1.52 g), and benzoic acid (818 mg). The reaction mixture was stirred at ambient temperature for 3 hrs. The resulting mixture was poured into water and extracted with ethyl acetate. The organic phase was sequentially washed with saturated aqueous ammonium chloride solution, saturated aqueous sodium hydrogen carbonate solution and brine. The resulting organic phase was dried over sodium sulfate, and the solvent was removed in vacuo to give Compound (9) as a pale yellow solid (2.6 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.23 (3H, t, J=7.1 Hz), 2.93 (6H, s), 3.52 (2H, m), 5.48 (1H, s), 6.36 (1H, d, J=7.7 Hz), 6.61 (1H, d, J=8.6 Hz), 6.68 (2H, d, J=8.9 Hz), 7.13 (2H, d, J=8.9 Hz), 7.33 (2H, m), 7.45 (3H, m), 7.80 (2H, d, J=8.5 Hz);
MASS (ES+): m/e 433 (M+1).

Preparation 10

Compound (10) (1.64 g) was obtained in a manner similar to Preparation 5.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.95 (6H, s), 6.36 (1H, d, J=6.9 Hz), 6.64 (1H, d, J=8.0 Hz), 6.69 (2H, d, J=8.8 Hz), 7.11 (2H, d, J=8.8 Hz), 7.44 (2H, m), 7.51 (3H, m), 7.84 (4H, m), 9.99 (1H, s);

MASS (ES+): m/e 359 (M+1).

Preparation 11

Compound (11) (1.95 g) was obtained in a manner similar to Preparation 6.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.34 (3H, t, J=7.1 Hz), 2.94 (6H, s), 4.26 (2H, q, J=7.2 Hz), 6.33 (1H, d, J=7.3 Hz), 6.40 (1H, d, J=16.0 Hz), 6.50 (1H, d, J=6.9 Hz), 6.69 (2H, d, J=8.8 Hz);

MASS (ES+): m/e 429 (M+1).

Preparation 12

Compound (12) (1.79 g) was obtained in a manner similar to Preparation 7.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.95 (6H, s), 6.34 (1H, d, J=16.0 Hz), 6.63 (1H, d, J=7.4 Hz), 6.71 (2H, d, J=8.7 Hz), 7.14 (2H, d, J=8.5 Hz), 7.38 (2H, d, J=8.5 Hz), 7.38 (2H, d, J=8.0 Hz), 7.45 (2H, m), 7.51 (3H, m), 7.75 (1H, d, J=16.0 Hz), 7.83 (2H, d, J=6.6 Hz);

MASS (ES+): m/e 401 (M+1).

Preparation 13

Compound (13) (1.94 g) was obtained in a manner similar to Preparation 8. The obtained Compound (13) was used in Example 2.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.62 (3H, br), 1.85 (3H, br), 2.95 (6H, s), 3.65 (1H, br), 3.97 (1H, br), 5.01 (1H, br), 6.33 (1H, d, J=7.8 Hz), 6.64 (1H, d, J=6.9 Hz), 6.70 (2H, d, J=8.8 Hz), 7.13 (2H, d, J=8.8 Hz), 7.33 (2H, d, J=8.1 Hz), 7.46 (5H, m), 7.70 (1H, br, J=16.0 Hz), 7.82 (2H, d, J=8.1 Hz);

MASS (ES+): m/e 500 (M+1).

Preparation 14

To a solution of 1-(3-bromophenyl)ethanone (5.0 g) in ethanol (50 mL) were added hydroxylamine hydrochloride (3.49 g) and pyridine (30.5 mL), and the mixture was stirred at ambient temperature for 1 hr. The organic solvent was removed in vacuo,

and the residue was extracted with ethyl acetate. The organic phase was washed with saturated aqueous ammonium chloride solution and dried over sodium sulfate. The solvent was removed in vacuo to give Compound (14). The resulting crude product was used in the next reaction without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.26 (3H, s), 7.24 (1H, t, J=8.0 Hz), 7.49 (1H, ddd, J=8.0, 1.8, 1.1 Hz), 7.56 (1H, ddd, J=8.0, 1.8, 1.1 Hz), 7.80 (1H, t, J=1.8 Hz).

Preparation 15

To a solution of Compound (14) (5.38 g) in ethanol (54 mL) were added zinc powder (8.22 g), ammonium acetate (1.94 g) and aqueous ammonia (28%, 33.6 mL), and the mixture was refluxed for 1 hr. Additional aqueous ammonia (28%, 33.6 mL) was added to the mixture, and the mixture was refluxed for 2 hrs. The mixture was allowed to cool to ambient temperature and concentrated in vacuo. The residue was extracted with ethyl acetate. The organic phase was washed with saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was removed in vacuo to give a mixture of Compound (15) and 1-phenylethylamine (10:7, 3.7 g). The resulting crude product was used in the next reaction without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.38 (3H, d, J=7.0 Hz), 4.10 (1H, q, J=7.0 Hz), 7.19 (1H, t, J=7.7 Hz), 7.34 (1H, m), 7.51 (1H, t, J=1.8 Hz), 7.63 (1H, m).

Preparation 16

To a solution of the mixture of Compound (15) and 1-phenylethylamine (10:7, 3.71 g) in N,N-dimethylformamide (37 mL) were added benzoic acid (2.49 g), 1-hydroxybenzotriazole (3.26 g) and 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (WSCD-HCl, 4.62 g), and the mixture was stirred for 1 day. The reaction mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water, saturated aqueous ammonium chloride solution, saturated aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was removed in vacuo to give a mixture of Compound (16)

and N-(1-phenylethyl)benzamide (10:7, 2.65 g) as a colorless solid.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.58 (3H, d, J=7.0 Hz), 5.31 (1H, q, J=7.0 Hz), 6.34 (1H, br), 7.22 (1H, t, J=7.7 Hz), 7.28-7.54 (6H, m), 7.77 (2H, m).

Preparation 17

To a solution of the mixture of Compound (16) and N-(1-phenylethyl)benzamide (10:7, 2.65 g) in N,N-dimethylformamide (26.5 mL) were added acrylic acid (3.4 mL), palladium(II) acetate (97.8 mg), triphenylphosphine (457 mg) and N,N-diisopropylethylamine (4.55 mL), and the mixture was stirred at 100°C for 3 hrs. The resulting mixture was allowed to cool to ambient temperature and poured into 1N sodium hydroxide solution. The mixture was washed with ether, and the aqueous phase was acidified with 1N hydrogen chloride and extracted with ethyl acetate. The organic phase was washed with saturated aqueous ammonium chloride solution and brine, dried over sodium sulfate, and concentrated in vacuo. The residual yellow solid was triturated with diisopropyl ether to give Compound (17) as a colorless powder (731 mg).

^{1}H-NMR (300 MHz, $CDCl_3$/MeOH-d_4, δ): 1.63 (3H, d, J=7.0 Hz), 5.35 (1H, m), 6.44 (1H, d, J=16.0 Hz), 7.37-7.51 (6H, m), 7.55 (1H, s), 7.71 (1H, d, J=16.0 Hz), 7.78 (2H, d, J=7.6 Hz);

MASS (ES+): m/e 296 (M+1).

Preparation 18

Compound (18) (970 mg) was obtained in a manner similar to Preparation 8. The obtained Compound (18) was used in Example 3.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.62 (3H, d, J=7.0 Hz), 1.53-1.91 (6H, br), 3.66 (1H, m), 3.97 (1H, m), 5.00 (1H, br), 5.35 (1H, m), 6.36 (1H, m), 7.35-7.54 (7H, m), 7.72 (1H, d, J=16.0 Hz), 7.78 (2H, d, J=8.0 Hz);

MASS (ES+): m/e 395 (M+1).

Preparation 19

Compound (19) (8.4 g) was obtained in a manner similar to Preparation 1.

^{1}H-NMR (300 MHz, $CDCl_3$ δ): 1.26 (3H, t, J=7.0 Hz), 3.61 (4H, m), 5.15 (2H, s), 5.57 (1H, s), 7.04 (2H, d, J=8.8 Hz), 7.35-7.46 (5H, m), 7.58 (2H, d, J=8.5 Hz), 7.75 (2H, d, J=8.0 Hz), 7.82 (2H, d, J=8.8 Hz);

MASS (ES+): m/e 391 (M+1).

Preparation 20

Compound (20) (5.8 g) was obtained in a manner similar to Preparation 2.

Preparation 21

Compound (21) (5.7 g) was obtained in a manner similar to Preparation 3.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.22 (3H, t, J=7.0 Hz), 1.26 (3H, t, J=7.0 Hz), 3.49-3.65 (4H, m), 5.03 (2H, s), 5.17 (1H, s), 5.46 (1H, s), 6.91 (2H, d, J=8.9 Hz), 7.27 (2H, d, J=8.9 Hz), 7.31-7.43 (9H, m).

Preparation 22

Compound (22) (3.15 g) was obtained in a manner similar to Preparation 4.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 5.05 (2H, s), 6.08 (1H, d, J=7.1 Hz), 6.23 (1H, d, J=7.5 Hz), 6.94 (2H, d, J=8.8 Hz), 7.11 (2H, d, J=8.8 Hz), 7.31-7.43 (7H, m), 7.85 (2H, d, J=8.4 Hz), 9.99 (1H, s).

Preparation 23

Compound (23) (3.76 g) was obtained in a manner similar to Preparation 6.

Preparation 24

Compound (24) (2.06 g) was obtained in a manner similar to Preparation 7.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.00 (3H, s), 5.15 (2H, s), 6.13 (1H, d, J=8.5 Hz), 6.56 (1H, d, J=16.1 Hz), 7.04 (2H, d, J=8.9 Hz), 7.25 (2H, d, J=8.8 Hz), 7.36 (2H, d, J=8.5 Hz), 7.39-7.52 (5H, m), 7.63 (1H, d, J=16.1 Hz), 7.71 (2H, d, J=8.5 Hz), 8.88 (1H, d, J=8.7 Hz);

MASS (ES+): m/e 402.

Preparation 25

Compound (25) (1.35 g) was obtained in a manner similar to Preparation 8. The obtained Compound (25) was used in Example 4.
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.60 (3H, br), 1.85 (3H, br), 2.07 (3H, s), 3.66 (1H, br), 3.97 (1H, br), 5.00 (1H, br), 5.05 (2H, s), 6.06 (1H, d, J=8.4 Hz), 6.18 (1H, d, J=7.4 Hz), 6.92 (2H, d, J=8.7 Hz), 7.11 (2H, d, J=8.5 Hz), 7.23 (2H, d, J=8.0 Hz), 7.32-7.47 (8H, m), 7.69 (1H, d, J=15.8 Hz).

Preparation 26

Compound (26) (10.5 g) was obtained in a manner similar to Preparation 1.
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 4.07 (2H, m), 4.15 (2H, m), 5.89 (1H, s), 7.41 (1H, t, J=7.7 Hz), 7.49 (2H, t, J=7.4 Hz), 7.53 (1H, t, J=7.7 Hz), 7.65-7.75 (5H, m), 7.84 (1H, d, J=7.7 Hz), 7.89 (2H, d, J=8.0 Hz), 7.95 (1H, s);
MASS (ES+): m/e 331 (M+1).

Preparation 27

Compound (27) (6.7 g) was obtained in a manner similar to Preparation 2.

Preparation 28

Compound (28) (4.3 g) was obtained in a manner similar to Preparation 3.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.03 (2H, m), 4.12 (2H, m), 5.25 (1H, s), 5.76 (1H, s), 7.34 (1H, d, J=7.1 Hz), 7.41 (1H, t, J=7.6 Hz), 7.43 (1H, d, J=7.3 Hz), 7.50-7.58 (4H, m), 7.60 (1H, s), 7.66 (2H, d, J=8.5 Hz), 7.71 (2H, d, J=7.6 Hz).

Preparation 29

Compound (29) (1.44 g) was obtained in a manner similar to Preparation 4.
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.10 (3H, s), 4.03 (2H, m), 4.12 (2H, m), 5.79 (1H, s), 6.04 (1H, br), 6.32 (1H, d, J=8.0 Hz), 7.24-7.32 (3H, m), 7.33-7.46 (6H, m), 7.53-7.59 (4H, m);
MASS (ES+): m/z 392 ($M+H_2O+1$).

Preparation 30

Compound (30) (1.26 g) was obtained in a manner similar to Preparation 5.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.12 (3H, s), 6.13 (1H, d, J=7.6 Hz), 6.36 (1H, d, J=7.6 Hz), 7.28 (2H, d, J=8.1 Hz), 7.36 (1H, m), 7.44 (2H, t, J=7.0 Hz), 7.53-7.59 (6H, m), 7.82 (2H, m), 10.0 (1H, s);

MASS (ES+): m/e 330 (M+1).

Preparation 31

Compound (31) (1.53 g) was obtained in a manner similar to Preparation 6.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.32 (3H, t, J=7.0 Hz), 2.01 (3H, s), 4.24 (2H, q, J=7.0 Hz), 6.30 (1H, d, J=7.9 Hz), 6.40 (1H, d, J=16.0 Hz), 6.54 (1H, d, J=8.0 Hz);

MASS (ES+): m/z 400 (M+1).

Preparation 32

Compound (32) (1.28 g) was obtained in a manner similar to Preparation 7.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.05 (3H, s), 6.27 (1H, d, J=8.3 Hz), 6.61 (1H, d, J=16.0 Hz), 7.42-7.49 (4H, m), 7.54 (2H, t, J=7.5 Hz), 7.65 (1H, d, J=15.7 Hz), 7.66 (1H, m), 7.69-7.74 (4H, m), 7.79 (1H, s), 8.96 (1H, d, J=8.4 Hz);

MASS (ES-): m/z 370 (M-1).

Preparation 33

Compound (33) (1.20 g) was obtained in a manner similar to Preparation 8. The obtained Compound (33) was used in Example 5.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.53 (3H, br), 1.67 (3H, br), 1.96 (3H, s), 3.72 (1H, br), 3.94 (1H, br), 4.90 (1H, s), 6.18 (1H, d, J=8.2 Hz), 6.49 (1H, d, J=16.1 Hz), 7.33-7.40 (5H, m), 7.43-7.48 (4H, m), 7.57 (1H, br), 7.62-7.66 (4H, m), 8.88 (1H, d, J=8.4 Hz).

Preparation 34

To a solution of 1,1'-biphenyl-4-yl[3-(1,3-dioxolan-2-yl)phenyl]methylamine in dichloromethane (20 mL) were added methanesulfonyl chloride and N-ethyl-N,N-diisopropylamine at 5°C, and the mixture was stirred at 5°C for 5 min. The mixture was warmed to ambient temperature and stirred for 30 min. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous ammonium chloride solution, water, saturated

aqueous sodium hydrogen carbonate solution and brine, and dried over sodium sulfate. The solvent was removed in vacuo to give Compound (34) (1.82 g), which was used in the next reaction without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.72 (3H, s), 4.04 (2H, m), 4.12 (2H, m), 5.06 (1H, d, J=7.0 Hz), 5.78 (1H, s), 5.83 (1H, d, J=7.4 Hz), 7.32-7.47 (8H, m), 7.51 (1H, s), 7.54-7.60 (4H, m);
MASS (ES+): m/z 410 (M+1).

Preparation 35

Compound (35) (1.56 g) was obtained in a manner similar to Preparation 5.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.79 (3H, s), 5.07 (1H, d, J=7.2 Hz), 5.90 (1H, d, J=6.9 Hz), 7.37 (3H, m), 7.45 (2H, d, J=7.4 Hz), 7.55-7.63 (5H, m), 7.68 (1H, d, J=7.7 Hz), 7.85 (1H, d, J=7.5 Hz), 7.91 (1H, s), 10.02 (1H, s);
MASS (ES-): m/z 364 (M-1).

Preparation 36

Compound (36) (3.24 g) was obtained in a manner similar to Preparation 6.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.32 (3H, t, J=7.0 Hz), 2.77 (3H, s), 4.24 (2H, q, J=7.0 Hz), 5.14 (1H, d, J=7.0 Hz), 5.84 (1H, d, J=7.0 Hz), 6.44 (1H, d, J=15.8 Hz);
MASS (ES+): m/z 436 (M+1).

Preparation 37

Compound (37) (1.55 g) was obtained in a manner similar to Preparation 7.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.81 (3H, s), 5.82 (1H, d, J=9.6 Hz), 6.37 (1H, d, J=16.0 Hz), 7.44 (1H, m), 7.50-7.62 (6H, m), 7.73 (4H, m), 7.66 (2H, m), 7.93 (1H, s), 8.50 (1H, d, J=9.5 Hz);
MASS (ES+): m/z 406 (M-1).

Preparation 38

Compound (38) (1.28 g) was obtained in a manner similar to Preparation 8. The obtained Compound (38) was used in Example 6.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.53 (3H, br), 1.69 (3H, br), 2.73 (3H, s), 3.53 (1H, br), 3.94 (1H, br), 4.91 (1H, br), 5.73 (1H, br),

6.51 (1H, d, J=16.1 Hz), 7.36 (1H, m), 7.43-7.51 (8H, m), 7.72 (1H, s), 8.41 (1H, br).

Preparation 39

Compound (39) (5.05 g) was obtained in a manner similar to Preparation 1.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 4.06 (2H, m), 4.14 (2H, m), 5.86 (1H, s), 7.47 (2H, d, J=8.0 Hz), 7.52 (1H, d, J=7.5 Hz), 7.72 (2H, d, J=7.1 Hz), 7.77 (2H, d, J=7.2 Hz), 7.89 (1H, s).

Preparation 40

Compound (40) (5.95 g) was obtained in a manner similar to Preparation 2.

Preparation 41

Compound (41) (4.43 g) was obtained in a manner similar to Preparation 3.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 4.04 (2H, m), 4.13 (2H, m), 5.21 (1H, s), 5.78 (1H, s), 7.27-7.38 (6H, m), 7.49 (1H, s);

MASS (ES+): m/e 273 ($M-NH_2$).

Preparation 42

Compound (42) (2.42 g) was obtained in a manner similar to Preparation 9.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 4.03 (2H, m), 4.11 (2H, m), 5.77 (1H, s), 6.44 (1H, d, J=7.7 Hz), 6.63 (1H, br.d, J=8.4 Hz), 7.23 (2H, d, J=7.4 Hz), 7.32 (2H, d, J=8.7 Hz), 7.35-7.55 (6H, m), 7.80 (2H, d, J=7.0 Hz);

MASS (ES+): m/e 394 (M+1).

Preparation 43

Compound (43) (1.86 g) was obtained in a manner similar to Preparation 5.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 6.49 (1H, d, J=7.6 Hz), 6.65 (1H, br.d, J=7.6 Hz), 7.23 (2H, d, J=8.4 Hz), 7.35 (2H, d, J=8.5 Hz), 7.46 (2H, t, J=7.4 Hz), 7.55 (2H, t, J=7.1 Hz), 7.58 (1H, d, J=8.5 Hz), 7.82 (4H, m), 10.00 (1H, s);

MASS (ES+): m/e 350 (M+1).

Preparation 44

Compound (44) (2.23 g) was obtained in a manner similar to

Preparation 11.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.33 (3H, t, J=7.1 Hz), 4.25 (2H, q, J=7.1 Hz), 6.40 (1H, d, J=15.7 Hz), 6.44 (1H, d, J=7.0 Hz).

Preparation 45

Compound (45) (1.82 g) was obtained in a manner similar to Preparation 7.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 6.39 (1H, d, J=16.2 Hz), 6.44 (1H, d, J=7.3 Hz), 7.05 (1H, br), 7.24 (2H, d, J=8.0 Hz), 7.30-7.40 (4H, m), 7.42-7.56 (5H, m), 7.65 (1H, d, J=15.7 Hz), 7.83 (2H, d, J=7.0 Hz).

Preparation 46

Compound (46) (2.09 g) was obtained in a manner similar to Preparation 8. The obtained Compound (46) was used in Example 7.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.62 (3H, br), 1.82 (3H, br), 3.65 (1H, m), 3.95 (1H, m), 4.97 (1H, br), 6.42 (1H, d, J=7.0 Hz), 6.82 (1H, br.d, J=7.0 Hz), 7.22 (2H, d, J=8.5 Hz), 7.29-7.56 (8H, m), 7.63 (1H, d, J=15.7 Hz), 7.83 (2H, d, J=7.0 Hz);

MASS (ES+): m/e 491 (M+1).

Preparation 47

Compound (47) (2.5 g) was obtained in a manner similar to Preparation 4.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 4.04 (2H, m), 4.11 (2H, m), 5.76 (1H, s), 6.03 (1H, br.d, J=8.3 Hz), 6.24 (1H, d, J=8.1 Hz), 7.17 (3H, m), 7.17-7.45 (5H, m);

MASS (ES+): m/e 332 (M+1).

Preparation 48

Compound (48) (1.98 g) was obtained in a manner similar to Preparation 5.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.09 (3H, s), 6.10 (1H, br, J=7.3 Hz), 6.29 (1H, d, J=7.6 Hz), 7.15 (2H, d, J=8.4 Hz), 7.32 (2H, d, J=8.5 Hz), 7.49 (1H, d, J=7.8 Hz), 7.53 (1H, t, J=7.6 Hz), 7.75 (1H, s), 7.80 (1H, d, J=6.7 Hz), 9.99 (1H, s);

MASS (ES-): m/e 286 (M-1).

Preparation 49

Compound (49) (2.41 g) was obtained in a manner similar to

Preparation 6.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.33 (3H, t, J=7.1 Hz), 2.09 (3H, s), 4.26 (2H, q, J=7.1 Hz), 6.02 (1H, br, J=8.4 Hz), 6.23 (1H, d, J=8.4 Hz), 6.40 (1H, d, J=16.1 Hz).

Preparation 50

Compound (50) (2.27 g) was obtained in a manner similar to Preparation 7.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.08 (3H, s), 6.22 (1H, m), 6.39 (1H, d, J=16.0 Hz), 7.17 (2H, d, J=8.4 Hz), 7.24 (1H, d, J=7.8 Hz), 7.31 (2H, d, J=8.6 Hz), 7.36 (1H, t, J=7.8 Hz), 7.38 (1H, s), 7.45 (1H, d, J=7.6 Hz), 7.64 (1H, d, J=16.0 Hz).

Preparation 51

Compound (51) (2.76 g) was obtained in a manner similar to Preparation 8. The obtained Compound (51) was used in Example 8.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.55-1.71 (3H, br), 1.77-1.93 (3H, br), 2.09 (3H, s), 3.65 (1H, m), 3.97 (1H, m), 4.99 (1H, m), 6.22 (1H, d, J=8.7 Hz), 6.30 (1H, br), 7.15 (2H, d, J=8.5 Hz), 7.20 (1H, m), 7.27 (2H, d, J=8.0 Hz), 7.33 (1H, s), 7.34-7.44 (1H, m), 7.64 (1H, d, J=15.9 Hz);

MASS (ES+): m/e 429 (M+1).

Preparation 52

Compound (52) (1.65 g) was obtained in a manner similar to Preparation 9.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.40 (3H, t, J=7.0 Hz), 4.01 (2H, q, J=7.0 Hz), 4.00 (2H, m), 4.09 (2H, m), 5.77 (1H, s), 6.42 (1H, d, J=7.5 Hz), 6.64 (1H, d, J=7.8 Hz), 6.85 (2H, d, J=8.4 Hz), 7.18 (2H, d, J=8.4 Hz), 7.30 (1H, d, J=7.3 Hz), 7.36 (1H, t, J=7.7 Hz), 7.41 (1H, br.s), 7.44 (2H, d, J=7.6 Hz), 7.50 (1H, d, J=7.0 Hz), 7.80 (2H, d, J=8.5 Hz);

MASS (ES+): m/e 404 (M+1).

Preparation 53

Compound (53) (1.50 g) was obtained in a manner similar to Preparation 5.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.41 (3H, t, J=7.0 Hz), 4.02 (2H, q, J=7.0 Hz), 6.44 (1H, d, J=7.3 Hz), 6.69 (1H, d, J=7.3 Hz), 6.87

(2H, d, J=8.8 Hz), 7.17 (2H, d, J=8.8 Hz), 7.44 (2H, m), 7.49-7.55 (2H, m), 7.60 (1H, d, J=7.8 Hz), 7.81 (4H, m), 9.98 (1H, s).

Preparation 54

Compound (54) (1.80 g) was obtained in a manner similar to Preparation 6.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.32 (3H, t, J=7.1 Hz), 1.41 (3H, t, J=6.9 Hz), 4.02 (2H, q, J=6.9 Hz), 4.24 (2H, q, J=7.1 Hz), 6.38 (1H, d, J=16.3 Hz), 6.40 (1H, d, J=7.0 Hz), 6.74 (1H, d, J=7.4 Hz), 6.86 (2H, d, J=8.7 Hz), 7.18 (2H, d, J=8.8 Hz).

Preparation 55

Compound (55) (1.49 g) was obtained in a manner similar to Preparation 7.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.41 (3H, t, J=7.0 Hz), 4.03 (2H, q, J=7.0 Hz), 6.38 (1H, d, J=16.1 Hz), 6.40 (1H, d, J=7.4 Hz), 6.88 (2H, d, J=8.8 Hz), 7.09 (21H, d, J=8.1 Hz), 7.19 (2H, d, J=8.3 Hz), 7.36 (2H, m), 7.41-7.48 (4H, m), 7.53 (1H, m), 7.65 (1H, d, J=15.8 Hz), 7.83 (2H, d, J=7.0 Hz).

Preparation 56

Compound (56) (1.74 g) was obtained in a manner similar to Preparation 8. The obtained Compound (56) was used in Example 9.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.41 (3H, t, J=7.0 Hz), 1.60 (3H, br), 1.82 (3H, br), 3.64 (1H, br), 3.96 (1H, br), 4.02 (2H, q, J=7.0 Hz), 4.98 (1H, br), 6.39 (1H, d, J=8.0 Hz), 6.72 (1H, d, J=8.0 Hz), 6.87 (1H, d, J=8.8 Hz), 7.17 (2H, d, J=8.8 Hz), 7.32 (2H, m), 7.36-7.47 (4H, m), 7.52 (1H, m), 7.65 (1H, d, J=15.7 Hz), 7.82 (2H, d, J=7.5 Hz);

MASS (ES+): m/e 501 (M+1).

Preparation 57

Compound (57) (6.7 g) was obtained in a manner similar to Preparation 1.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.46 (3H, t, J=7.0 Hz), 4.07 (2H, m), 4.14 (2+2H, m), 5.87 (1H, s), 6.95 (2H, d, J=8.7 Hz), 7.50 (1H, t, J=7.5 Hz), 7.69 (1H, d, J=7.7 Hz), 7.76 (1H, d, J=7.7 Hz), 7.81 (2H, d, J=8.8 Hz), 7.87 (1H, s).

Preparation 58

Compound (58) (3.72 g) was obtained in a manner similar to Preparation 2.

MASS (ES+): m/e 314 (M+1).

Preparation 59

Compound (59) (3.42 g) was obtained in a manner similar to Preparation 3.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.39 (3H, t, J=7.0 Hz), 4.00 (2H, q, J=7.0 Hz), 4.02 (2H, m), 4.12 (2H, m), 5.18 (1H, s), 5.78 (1H, s), 6.82 (2H, d, J=8.7 Hz), 7.25 (2H, d, J=8.2 Hz), 7.34 (3H, m), 7.51 (1H, br.s);

MASS (ES+): m/e 283 ($M-NH_2$).

Preparation 60

Compound (60) (2.42 g) was obtained in a manner similar to Preparation 4.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.40 (3H, t, J=6.9 Hz), 2.06 (3H, s), 4.01 (2H, q, J=6.9 Hz), 4.03 (2H, m), 4.10 (2H, m), 5.77 (1H, s), 6.01 (1H, d, J=7.3 Hz), 6.22 (1H, d, J=8.1 Hz), 6.83 (2H, d, J=8.8 Hz), 7.11 (2H, d, J=8.6 Hz), 7.21 (1H, d, J=7.3 Hz), 7.41-7.88 (3H, m);

MASS (ES+): m/e 342 (M+1).

Preparation 61

Compound (61) (1.69 g) was obtained in a manner similar to Preparation 5.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.41 (3H, t, J=7.0 Hz), 2.10 (3H, s), 4.02 (2H, q, J=7.0 Hz), 6.02 (1H, d, J=6.9 Hz), 6.25 (1H, d, J=7.3 Hz), 6.86 (2H, d, J=8.7 Hz), 7.10 (2H, d, J=8.9 Hz), 7.52 (2H, m), 7.78 (2H, m), 10.00 (1H, s).

Preparation 62

Compound (62) (2.09 g) was obtained in a manner similar to Preparation 6.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.32 (3H, t, J=7.1 Hz), 1.40 (3H, t, J=7.0 Hz), 2.06 (3H, s), 4.00 (2H, q, J=6.9 Hz), 4.24 (2H, q, J=7.1 Hz), 6.20 (1H, d, J=8.2 Hz), 6.38 (1H, d, J=16.1 Hz), 6.40 (1H, d, J=6.5 Hz), 6.83 (2H, d, J=8.9 Hz), 7.11 (2H, d, J=8.8 Hz).

Preparation 63

Compound (63) (1.84 g) was obtained in a manner similar to Preparation 7.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.41 (3H, t, J=7.0 Hz), 2.07 (3H, s), 4.02 (2H, q, J=7.0 Hz), 6.18 (1H, m), 6.39 (1H, d, J=16.0 Hz), 6.85 (2H, d, J=8.8 Hz), 7.12 (2H, d, J=8.4 Hz), 7.27 (1H, d, J=8.4 Hz), 7.27 (1H, d, J=7.7 Hz), 7.35 (1H, t, J=7.8 Hz), 7.40 (1H, s), 7.44 (1H, d, J=7.8 Hz), 7.64 (1H, d, J=16.0 Hz).

Preparation 64

Compound (64) (1.69 g) was obtained in a manner similar to Preparation 8. The obtained Compound (64) was used in Example 10.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.41 (3H, t, J=7.0 Hz), 1.61 (3H, br), 1.85 (3H, br), 2.08 (3H, s), 3.65 (1H, br), 3.97 (1H, br), 4.01 (2H, q, J=7.0 Hz), 5.00 (1H, br), 6.09 (1H, br), 6.19 (1H, d, J=8.5 Hz), 6.85 (2H, d, J=8.4 Hz), 7.10 (2H, d, J=8.8 Hz), 7.23 (1H, d, J=7.6 Hz), 7.24-7.30 (3H, m), 7.67 (1H, d, J=15.8 Hz); MASS (ES-): m/e 437 (M-1).

Preparation 65

Compound (65) (1.12 g) was obtained in a manner similar to Preparation 5.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 5.96 (2H, s), 6.40 (1H, d, J=7.0 Hz), 6.67 (1H, d, J=7.0 Hz), 6.73 (1H, s), 6.78 (2H, m), 7.43-7.55 (4H, m), 7.59 (1H, d, J=7.6 Hz), 7.82 (4H, m), 9.99 (1H, s).

Preparation 66

Compound (66) (1.34 g) was obtained in a manner similar to Preparation 6.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.33 (3H, t, J=7.0 Hz), 4.25 (2H, q, J=7.0 Hz), 5.97 (2H, s), 6.36 (1H, d, J=8.4 Hz), 6.40 (1H, d, J=16.1 Hz), 6.61 (1H, br), 6.75 (1H, s), 6.78 (2H, s).

Preparation 67

Compound (67) (856 mg) was obtained in a manner similar to Preparation 7.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 5.97 (2H, s), 6.36 (1H, d, J=7.7 Hz), 6.39 (1H, d, J=16.0 Hz), 6.77 (1H, s), 6.79 (2H, s), 7.33-7.55 (8H, m), 7.65 (1H, d, J=16.0 Hz), 7.83 (2H, d, J=7.0 Hz).

Preparation 68

Compound (68) (988 mg) was obtained in a manner similar to Preparation 8. The obtained Compound (68) was used in Example 11.
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.59 (3H, br), 1.82 (3H, br), 3.64 (1H, m), 3.95 (1H, m), 4.98 (1H, br.s), 5.95 (2H, s), 6.34 (1H, d, J=8.0 Hz), 6.74 (1H, s), 6.77 (2H, s), 7.31-7.55 (8H, m), 7.63 (1H, m), 7.83 (2H, d, J=7.0 Hz).

Preparation 69

Compound (69) (2.61 g) was obtained in a manner similar to Preparation 1.
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 4.06 (2H, m), 4.13 (2H, m), 5.87 (1H, s), 6.07 (2H, s), 6.86 (1H, d, J=8.4 Hz), 7.36 (2H, m), 7.49 (1H, t, J=7.6 Hz), 7.69 (1H, d, J=8.0 Hz), 7.74 (1H, d, J=7.7 Hz), 7.86 (1H, s).

Preparation 70

Compound (70) (3.65 g) was obtained in a manner similar to Preparation 2.
MASS (ES-): m/e 314 (M+1).

Preparation 71

Compound (71) (2.22 g) was obtained in a manner similar to Preparation 3.
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 4.03 (2H, m), 4.13 (2H, m), 5.15 (1H, s), 5.78 (1H, s), 5.91 (2H, s), 6.73 (1H, d, J=8.4 Hz), 6.84 (2H, m), 7.34 (3H, m), 7.50 (1H, s).

Preparation 72

Compound (72) (1.39 g) was obtained in a manner similar to Preparation 9.
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 3.99-4.06 (2H, m), 4.06-4.17 (2H, m), 5.78 (1H, s), 5.94 (1H, s), 6.37 (1H, d, J=7.8 Hz), 6.62 (1H, d, J=7.8 Hz), 6.76 (1H, s), 6.77 (2H, s), 7.29 (1H, d, J=7.4 Hz), 7.37 (1H, t, J=7.2 Hz), 7.41-7.54 (4H, m), 7.62 (1H, t, J=8.0 Hz), 7.8 (2H, d, J=7.0 Hz).

Preparation 73

Compound (73) (1.41 g) was obtained in a manner similar to Preparation 4.
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.06 (3H, s), 4.02 (2H, m), 4.13 (2H,

m), 5.77 (1H, s), 5.94 (2H, s), 6.02 (1H, br.d, J=8.1 Hz), 6.17 (1H, d, J=8.1 Hz), 6.68 (1H, s), 9.72 (1H, d, J=8.0 Hz), 6.74 (1H, t, J=8.0 Hz), 7.21 (1H, d, J=8.0 Hz), 7.28-7.42 (3H, m);
MASS (ES+): m/e 342 (M+1).

Preparation 74

Compound (74) (1.11 g) was obtained in a manner similar to Preparation 5.
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.09 (3H, s), 5.96 (2H, s), 6.05 (1H, br.d, J=8.0 Hz), 6.21 (1H, d, J=8.0 Hz), 6.67 (2H, m), 6.77 (1H, d, J=7.8 Hz), 7.51 (2H, m), 7.78 (2H, m), 9.99 (1H, s).

Preparation 75

Compound (75) (1.37 g) was obtained in a manner similar to Preparation 6.
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.33 (3H, t, J=7.0 Hz), 2.09 (3H, s), 4.26 (2H, q, J=7.0 Hz), 5.96 (2H, s), 6.00 (1H, br), 6.16 (1H, d, J=7.9 Hz), 6.69 (2H, d, J=9.6 Hz), 6.77 (1H, d, J=8.1 Hz).

Preparation 76

Compound (76) (973 mg) was obtained in a manner similar to Preparation 7.
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.07 (3H, s), 5.95 (2H, s), 6.14 (1H, s), 6.39 (1H, d, J=16.0 Hz), 6.69 (1H, s), 6.70 (1H, d, J=7.7 Hz), 6.75 (1H, t, J=8.8 Hz), 7.26 (1H, d, J=6.8 Hz), 7.35 (1H, t, J=7.7 Hz), 7.40 (1H, s), 7.44 (1H, d, J=7.6 Hz), 7.62 (1H, m), 7.65 (1H, d, J=16.0 Hz).

Preparation 77

Compound (77) (1.35 g) was obtained in a manner similar to Preparation 8. The obtained Compound (77) was used in Example 12.
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.72-1.56 (3H, br), 1.92-1.83 (3H, br), 3.65 (1H, m), 3.99 (1H, m), 5.00 (1H, m), 5.95 (2H, s), 6.14 (1H, s), 6.36 (1H, br), 6.68 (1H, s), 6.69 (1H, d, J=8.1 Hz), 6.77 (1H, d, J=7.8 Hz), 7.21 (1H, d, J=8.7 Hz), 7.33 (1H, t, J=7.4 Hz), 7.38 (1H, s), 7.40 (1H, d, J=8.0 Hz), 7.65 (1H, d, J=16.8 Hz);
MASS (ES-): m/e 437 (M-1).

Preparation 78

Compound (78) (3.2 g) was obtained in a manner similar to

Preparation 1.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.24 (6H, t, J=7.0 Hz), 3.57 (4H, m), 4.22 (2H, s), 5.04 (2H, s), 5.53 (1H, s), 6.93 (2H, d, J=8.5 Hz), 7.18 (2H, d, J=8.5 Hz), 7.29-7.43 (5H, m), 7.56 (2H, d, J=8.4 Hz), 8.00 (2H, d, J=8.4 Hz).

Preparation 79

To a suspension of 2-[4-(benzyloxy)phenyl]-1-[4-(diethoxymethyl)phenyl]ethanone (1.5 g) was added sodium borohydride (140 mg) at 5°C, and immediately after that, the mixture was allowed to warm to ambient temperature and stirred for 1 hr. The solvent was removed in vacuo, and the residue was diluted with ethyl acetate. The organic phase was sequentially washed with water, saturated aqueous ammonium chloride solution and brine, and dried over sodium sulfate. The solvent was removed in vacuo to give Compound (79) (1.51 g) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.24 (6H, t, J=7.0 Hz), 1.94 (1H, d, J=3.0 Hz), 2.90 (1H, dd, J=13.6, 8.4 Hz), 2.98 (1H, dd, J=13.6, 4.8 Hz), 3.48-3.67 (4H, m), 4.86 (1H, m), 5.05 (2H, s), 5.51 (1H, s), 6.91 (2H, d, J=8.7 Hz), 7.11 (2H, d, J=8.7 Hz), 7.32-7.39 (5H, m), 7.40-7.47 (4H, m).

Preparation 80

Compound (80) (838 mg) was obtained in a manner similar to Preparation 5.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.10 (1H, d, J=3.4 Hz), 2.90 (2H, dd, J=13.6, 8.3 Hz), 3.01 (2H, dd, J=13.6, 4.7 Hz), 4.94 (1H, m), 5.05 (2H, s), 6.93 (2H, d, J=8.5 Hz), 7.08 (2H, d, J=8.5 Hz), 7.33-7.45 (5H, m), 7.50 (2H, d, J=8.0 Hz), 7.85 (2H, d, J=8.0 Hz), 10.00 (1H, s).

Preparation 81

Compound (81) (1.01 g) was obtained in a manner similar to Preparation 6.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.34 (3H, t, J=7.0 Hz), 2.01 (1H, d, J=3.4 Hz), 2.90 (1H, dd, J=13.6, 8.3 Hz), 2.99 (1H, dd, J=13.6, 5.0 Hz), 4.27 (2H, q, J=7.0 Hz), 4.87 (1H, m), 5.05 (2H, s), 6.43 (1H, d, J=16.0 Hz), 6.92 (2H, d, J=8.9 Hz), 7.09 (2H, d, J=8.9

Hz), 7.32-7.45 (7H, m), 7.50 (2H, d, J=8.3 Hz), 7.68 (1H, d, J=16.0 Hz).

Preparation 82

Compound (82) (300 mg) was obtained in a manner similar to Preparation 7.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.81 (2H, m), 4.65 (1H, t, J=6.6 Hz), 5.04 (2H, s), 6.41 (1H, d, J=8.8 Hz), 7.05 (2H, d, J=8.8 Hz), 7.23-7.48 (10H, m).

Preparation 83

Compound (83) (337 mg) was obtained in a manner similar to Preparation 8. The obtained Compound (83) was used in Example 13.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.50-1.75 (6H, br), 2.81 (2H, m), 3.54 (1H, m), 3.96 (1H, m), 4.71 (1H, m), 4.90 (1H, s), 5.04 (2H, s), 5.31 (1H, d, J=4.5 Hz), 6.46 (1H, d, J=16.0 Hz), 6.86 (2H, d, J=8.6 Hz), 7.05 (2H, d, J=8.6 Hz), 7.35-7.50 (10H, m).

Preparation 84

To a solution of Compound (81) (394 mg) in N,N-dimethylformamide (8 mL) was added sodium hydride (60% in oil, 43.1 mg) at 5°C, and the mixture was stirred for 15 min. To the resulting mixture was added methyl iodide (0.091 mL) at 5°C, and the mixture was allowed to warm to ambient temperature and stirred for 3 hrs. The reaction mixture was poured into saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water, saturated aqueous ammonium chloride solution and brine, and dried over sodium sulfate. The solvent was removed in vacuo, and the residue was purified by preparative TLC (silica gel, hexane:ethyl acetate=2:1) to give Compound (84) (272 mg) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.38 (3H, t, J=7.0 Hz), 2.82 (1H, dd, J=13.6, 6.2 Hz), 3.04 (1H, dd, J=13.6, 6.9 Hz), 3.21 (3H, s), 4.27 (2H, q, J=7.0 Hz), 4.29 (1H, m), 5.03 (2H, s), 6.44 (1H, d, J=16.0 Hz), 6.85 (2H, d, J=8.4 Hz), 6.98 (2H, d, J=8.4 Hz), 7.22 (2H, d, J=8.0 Hz), 7.33-7.49 (7H, m), 7.68 (1H, d, J=16.0 Hz).

Preparation 85

Compound (85) (160 mg) was obtained in a manner similar to Preparation 7.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.82 (1H, dd, J=15.3, 5.8 Hz), 3.06 (1H, dd, J=15.3, 6.7 Hz), 3.21 (3H, s), 4.31 (1H, t, J=8.3 Hz), 5.03 (2H, s), 6.44 (1H, d, J=16.0 Hz), 6.84 (2H, d, J=8.7 Hz), 6.98 (2H, d, J=8.7 Hz), 7.23 (2H, d, J=8.4 Hz), 7.32-7.44 (5H, m), 7.49 (2H, d, J=8.4 Hz), 7.76 (1H, d, J=16.0 Hz).

Preparation 86

Compound (86) (195 mg) was obtained in a manner similar to Preparation 8. The obtained Compound (86) was used in Example 14.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.55-1.88 (6H, br), 2.81 (1H, dd, J=13.8, 6.1 Hz), 3.05 (1H, dd, J=13.8, 7.2 Hz), 3.20 (3H, s), 3.66 (1H, m), 3.97 (1H, m), 4.29 (1H, t, J=6.6 Hz), 5.02 (2+1H, s), 6.83 (2H, d, J=8.5 Hz), 6.97 (2H, d, J=8.5 Hz), 7.20 (2H, d, J=8.1 Hz), 7.31-7.47 (7H, m), 7.73 (1H, d, J=16.0 Hz);

MASS (ES+): m/e 488 (M+1).

Preparation 87

Compound (87) (1.69 g) was obtained in a manner similar to Preparation 1.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 3.08 (6H, s), 3.99-4.17 (4H, m), 5.87 (1H, s), 6.68 (2H, d, J=9.2 Hz), 7.47 (1H, dd, J=7.7, 7.7 Hz), 7.65 (1H, ddd, J=7.7, 1.4, 1.4 Hz), 7.72 (1H, ddd, J=7.7, 1.4, 1.4 Hz), 7.75-7.86 (3H, m);

MASS (ES+): m/e 298.13 (M+1).

Preparation 88

Compound (88) (6.0 g) was obtained in a manner similar to Preparation 2.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.91 (4H, s), 2.95 (2H, s), 3.89-4.07 (4H, m), 5.71 (0.3H, s), 5.74 (0.7H, s), 6.64-6.76 (2H, m), 7.15-7.31 (3H, m), 7.36-7.50 (3H, m), 10.84 (0.7H, s), 11.14 (0.3H, s);

MASS (ES+): m/e 313.16 (M+1).

Preparation 89

Compound (89) (5.03 g) was obtained in a manner similar to Preparation 3.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.91 (6H, s), 3.96-4.16 (4H, m), 5.15 (1H, s), 5.78 (1H, s), 6.68 (2H, d, J=8.8 Hz), 7.20 (2H, d, J=8.8 Hz), 7.28-7.38 (3H, m), 7.52 (1H, s);

MASS (ES-): m/e 297.19 (M-1).

Preparation 90

Compound (90) (1.52 g) was obtained in a manner similar to Preparation 9.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.93 (6H, s), 3.95-4.13 (4H, m), 5.79 (1H, s), 6.39 (1H, d, J=8.4 Hz), 6.56-6.66 (1H, m), 6.68 (2H, d, J=8.4 Hz), 7.13 (2H, d, J=8.4 Hz), 7.24-7.54 (7H, m), 7.76-7.86 (2H, m);

MASS (ES+): m/e 403.20 (M+1).

Preparation 91

Compound (91) (1.21 g) was obtained in a manner similar to Preparation 10.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.87 (6H, s), 6.39 (1H, d, J=8.8 Hz), 6.70 (2H, d, J=8.8 Hz), 7.18 (2H, d, J=8.8 Hz), 7.44-7.63 (4H, m), 7.70 (1H, d, J=8.1 Hz), 7.81 (1H, d, J=7.7 Hz), 7.87-7.97 (3H, m), 9.24 (1H, d, J=8.8 Hz), 9.99 (1H, s);

MASS (ES+): m/e 359.24 (M+1).

Preparation 92

Compound (92) (1.92 g) was obtained in a manner similar to Preparation 11.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.32 (3H, t, J=7.0 Hz), 2.95 (6H, s), 4.24 (2H, q, J=7.0 Hz), 6.34 (1H, d, J=7.7 Hz), 6.39 (1H, d, J=16.1 Hz), 6.62 (1H, d, J=7.7 Hz), 6.69 (2H, d, J=8.4 Hz), 7.12 (2H, d, J=8.4 Hz), 7.33-7.39 (2H, m), 7.39-7.56 (5H, m), 7.65 (1H, d, J=16.1 Hz), 7.77-7.86 (1H, m);

MASS (ES+): m/e 429.15 (M+1).

Preparation 93

Compound (93) (1.30 g) was obtained in a manner similar to Preparation 12.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.86 (6H, s), 6.32 (1H, d, J=8.4 Hz), 6.50 (1H, d, J=16.1 Hz), 6.69 (2H, d, J=8.8 Hz), 7.17 (2H, d, J=8.8 Hz), 7.35-7.61 (7H, m), 7.73 (1H, s), 7.91 (2H, d, J=8.1

Hz), 9.13 (1H, d, J=8.4 Hz);
MASS (ES+): m/e 401.19 (M+1).

Preparation 94

Compound (94) (1.33 g) was obtained in a manner similar to Preparation 13. The obtained Compound (94) was used in Example 15.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.54-1.84 (6H, m), 2.95 (6H, s), 3.54-3.67 (1H, m), 3.97-4.09 (1H, m), 4.99 (1H, s), 6.41 (1H, d, J=8.4 Hz), 6.55 (1H, d, J=16.1 Hz), 6.79 (2H, d, J=8.8 Hz), 7.26 (2H, d, J=8.8 Hz), 7.45-7.72 (8H, m), 7.99-8.07 (2H, m), 9.26 (1H, d, J=8.4 Hz), 11.35 (1H, s);
MASS (ES+): m/e 500.19 (M+1).

Preparation 95

Compound (95) (1.27 g) was obtained in a manner similar to Preparation 4.
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.06 (3H, s), 2.93 (6H, s), 3.98-4.15 (4H, m), 5.79 (1H, s), 5.92-6.00 (1H, m), 6.20 (1H, d, J=8.1 Hz), 6.67 (2H, d, J=8.8 Hz), 7.06 (2H, d, J=8.8 Hz), 7.20-7.28 (1H, m), 7.29-7.43 (3H, m);
MASS (ES+): m/e 341.21 (M+1).

Preparation 96

Compound (96) (1.04 g) was obtained in a manner similar to Preparation 5.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.92 (3H, s), 2.85 (6H, s), 6.07 (1H, d, J=8.8 Hz), 6.67 (2H, d, J=8.8 Hz), 7.07 (2H, d, J=8.8 Hz), 7.52-7.62 (2H, m), 7.76-7.82 (2H, m), 8.74 (1H, d, J=8.8 Hz), 9.98 (1H, s);
MASS (ES+): m/e 297.23 (M+1).

Preparation 97

Compound (97) (2.38 g) was obtained in a manner similar to Preparation 6.
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.33 (3H, t, J=7.0 Hz), 2.07 (3H, s), 2.94 (6H, s), 4.25 (2H, q, J=7.0 Hz), 6.01 (1H, d, J=8.1 Hz), 6.15 (1H, d, J=8.1 Hz), 6.39 (1H, d, J=16.1 Hz), 6.67 (2H, d, J=8.8 Hz), 7.05 (2H, d, J=8.8 Hz), 7.27-7.71 (5H, m);
MASS (ES+): m/e 367.19 (M+1).

Preparation 98

Compound (98) (780 mg) was obtained in a manner similar to Preparation 7.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.91 (3H, s), 2.84 (6H, s), 6.00 (1H, d, J=8.8 Hz), 6.49 (1H, d, J=16.1 Hz), 6.66 (2H, d, J=8.8 Hz), 7.07 (2H, d, J=8.8 Hz), 7.26-7.39 (2H, m), 7.49-7.64 (3H, m), 8.66 (1H, d, J=8.8 Hz);

MASS (ES+): m/e 339.21 (M+1).

Preparation 99

Compound (99) (915 mg) was obtained in a manner similar to Preparation 8. The obtained Compound (99) was used in Example 16.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.55-1.84 (6H, m), 2.00 (3H, s), 2.94 (6H, s), 3.58-3.67 (1H, m), 3.98-4.10 (1H, m), 5.00 (1H, s), 6.09 (1H, d, J=8.4 Hz), 6.55 (1H, d, J=16.1 Hz), 6.76 (2H, d, J=8.8 Hz), 7.16 (2H, d, J=8.8 Hz), 7.32-7.39 (1H, m), 7.41-7.61 (4H, m), 8.77 (1H, d, J=8.4 Hz), 11.36 (1H, s);

MASS (ES+): m/e 438.22 (M+1).

Example 1

To a stirred solution of Compound (8) (2.08 g) in methanol (38 mL) was added a solution of hydrogen chloride in methanol (hydrogen chloride methanol reagent 10, 9.5 mL, manufactured by Tokyo Kasei Co., Ltd.), and the mixture was stirred at ambient temperature for 1 hr. The solvent was removed in vacuo. The residue was dissolved in saturated aqueous sodium hydrogen carbonate solution, and extracted with ethyl acetate under basic conditions. The organic phase was washed with water and brine, and dried over sodium sulfate. The solvent was removed in vacuo, and the residue was triturated with diisopropyl ether to give Compound E1 as a colorless powder (1.42 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.90 (3H, s), 2.85 (6H, s), 5.98 (1H, d, J=8.3 Hz), 6.41 (1H, d, J=15.8 Hz), 6.67 (2H, d, J=8.8 Hz), 7.05 (2H, d, J=8.5 Hz), 7.27 (2H, d, J=8.5 Hz), 7.41 (1H, d, J=15.8 Hz), 7.49 (2H, d, J=7.8 Hz), 83.66 (1H, d, J=8.9 Hz);

MASS (ES+): m/e 354 (M+1).

Example 2

Compound E2 (1.45 g) was obtained from Compound (13) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.86 (6H, s), 6.30 (1H, d, J=8.4 Hz), 6.42 (1H, d, J=15.8 Hz), 6.69 (2H, d, J=8.8 Hz), 7.16 (2H, d, J=8.9 Hz), 7.37 (2H, d, J=8.0 Hz), 7.49 (6H, m), 7.92 (2H, d, J=8.4 Hz), 9.16 (1H, d, J=8.8 Hz);

MASS (ES+): m/e 416 (M+1).

Example 3

Compound E3 (419.7 mg) was obtained from Compound (18) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.57 (3H, d, J=7.0 Hz), 5.25 (1H, dq, J=7.0, 7.0 Hz), 6.51 (1H, d, J=16.0 Hz), 7.28 (1H, d, J=16.0 Hz), 7.40 (3H, m), 7.58 (4H, m), 7.96 (2H, d, J=8.1 Hz), 8.96 (1H, d, J=7.5 Hz);

MASS (ES+): m/e 311 (M+).

Example 4

Compound E4 (2.4 g) was obtained from Compound (25) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.91 (3H, s), 5.08 (2H, s), 6.03 (1H, d, J=8.8 Hz), 6.36 (1H, d, J=16.1 Hz), 6.96 (2H, d, J=8.7 Hz), 7.10 (1H, d, J=16.1 Hz), 7.17 (2H, d, J=8.8 Hz), 7.21 (2H, d, J=8.4 Hz), 7.28-7.37 (2H, m), 7.38-7.41 (2H, m), 7.42-7.46 (3H, m), 8.71 (1H, d, J=8.8 Hz);

MASS (ES-): m/e 415 (M-1).

Example 5

Compound E5 (912 mg) was obtained from Compound (33) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.96 (3H, s), 6.17 (1H, d, J=8.4 Hz), 6.45 (1H, d, J=15.8 Hz), 7.31-7.48 (9H, m), 7.55 (1H, s), 7.61-7.65 (4H, m), 8.86 (1H, d, J=8.8 Hz);

MASS (ES-): m/e 385 (M-1).

Example 6

Compound E6 (980 mg) was obtained from Compound (38) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.72 (3H, s), 5.73 (1H, br), 6.46

(4H, d, J=16.0 Hz), 7.33-7.40 (1H, m), 7.42-7.50 (7H, m), 7.62-7.70 (6H, m), 8.41 (1H, br);

MASS (ES+): m/e 423.

Example 7

Compound E7 (1.31 g) was obtained from Compound (46) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 6.40 (1H, d, J=15.7 Hz), 6.42 (1H, d, J=8.8 Hz), 7.23 (1H, d, J=15.7 Hz), 7.30 (1H, d, J=7.6 Hz), 7.35 (1H, t, J=7.6 Hz), 7.40-7.44 (3H, m), 7.45-7.53 (3H, m), 7.55 (2H, br), 7.92 (2H, d, J=7.6 Hz), 9.31 (1H, d, J=8.4 Hz);

MASS (ES-): m/e 405 (M-1).

Example 8

Compound E8 (1.60 g) was obtained from Compound (51) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.94 (3H, s), 6.11 (1H, d, J=8.9 Hz), 6.38 (1H, d, J=16.0 Hz), 7.11 (1H, d, J=16.0 Hz), 7.16 (1H, d, J=7.6 Hz), 7.32 (2H, d, J=8.4 Hz), 7.34 (1H, m), 7.39 (1H, t, J=7.4 Hz), 7.40 (2H, d, J=8.8 Hz), 8.44 (1H, s), 8.84 (1H, d, J=8.8 Hz);

MASS (ES-): m/e 343 (M-1).

Example 9

Compound E9 (1.18 g) was obtained from Compound (56) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.31 (3H, t, J=7.0 Hz), 4.00 (2H, q, J=7.0 Hz), 6.36 (2H, d, J=8.4 Hz), 6.39 (1H, d, J=15.8 Hz), 6.9 (2H, d, J=8.4 Hz), 7.22 (1H, d, J=15.8 Hz), 7.26-7.40 (5H, m), 7.44-7.57 (4H, m), 7.92 (2H, d, J=7.0 Hz), 9.24 (1H, d, J=8.4 Hz);

MASS (ES+): m/e 417 (M+1).

Example 10

Compound E10 (813.6 mg) was obtained from Compound (64) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.30 (3H, t, J=7.0 Hz), 1.92 (3H, s), 3.98 (2H, q, J=7.0 Hz), 6.05 (1H, d, J=8.3 Hz), 6.40 (1H, d, J=16.0 Hz), 6.87 (2H, d, J=8.9 Hz), 7.17 (2H, d, J=8.4 Hz), 7.22

(1H, d, J=7.0 Hz), 7.29-7.41 (3H, m), 7.45 (1H, s), 8.74 (1H, d, J=8.8 Hz);

MASS (ES-): m/e 353 (M-1).

Example 11

Compound E11 (651.6 mg) was obtained from Compound (68) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 5.99 (2H, s), 6.34 (1H, d, J=8.3 Hz), 6.42 (1H, d, J=16.1 Hz), 6.88 (2H, s), 6.99 (1H, s), 7.33-7.59 (8H, m), 7.92 (2H, d, J=8.0 Hz), 9.20 (1H, d, J=8.9 Hz);

MASS (ES-): m/e 415 (M-1).

Example 12

Compound E12 (699.1 mg) was obtained from Compound (77) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.93 (3H, s), 5.98 (2H, s), 6.03 (1H, d, J=8.1 Hz), 6.38 (1H, d, J=15.8 Hz), 6.77 (1H, d, J=8.0 Hz), 6.85 (1H, s), 6.85 (1H, d, J=8.1 Hz), 7.16 (1H, d, J=16.1 Hz), 7.17 (1H, d, J=7.0 Hz), 7.29 (1H, t, J=7.4 Hz), 7.43 (1H, s), 8.73 (1H, d, J=8.9 Hz);

MASS (ES-): m/e 353 (M-1).

Example 13

Compound E13 (232.5 mg) was obtained from Compound (83) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.80 (2H, m), 4.68 (1H, br), 5.04 (2H, s), 5.25 (1H, br), 6.37 (1H, d, J=16.0 Hz), 6.86 (2H, d, J=8.5 Hz), 7.05 (2H, d, J=8.5 Hz), 7.17 (1H, d, J=16.0 Hz), 7.26 (2H, d, J=8.1 Hz), 7.30-7.45 (7H, m);

MASS (ES+): m/e 390 (M+1).

Example 14

Compound E14 (123.1 mg) was obtained from Compound (86) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.78 (1H, dd, J=14.0, 5.6 Hz), 2.95 (1H, dd, J=14.0, 7.7 Hz), 3.06 (3H, s), 4.34 (1H, d, J=6.4 Hz), 5.04 (2H, s), 6.40 (1H, d, J=16.0 Hz), 6.86 (2H, d, J=8.7 Hz), 7.04 (2H, d, J=8.7 Hz), 7.21 (1H, d, J=16.0 Hz), 7.23 (2H, d, J=8.1 Hz), 7.32-7.24 (7H, m);

MASS (ES+): m/e 404 (M+1).

Example 15

Compound E15 (844 mg) was obtained from Compound (94) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.95 (6H, s), 6.40 (1H, d, J=8.4 Hz), 6.50 (1H, d, J=15.4 Hz), 6.79 (2H, d, J=8.8 Hz), 7.26 (2H, d, J=8.8 Hz), 7.39-7.70 (8H, m), 7.99-8.05 (2H, m), 9.26 (1H, d, J=8.4 Hz);

MASS (ES+): m/e 416.16 (M+1).

Example 16

Compound E16 (440 mg) was obtained from Compound (99) in a manner similar to Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.01 (3H, s), 2.94 (6H, s), 6.08 (1H, d, J=9.1 Hz), 6.51 (1H, d, J=15.4 Hz), 6.76 (2H, d, J=8.8 Hz), 7.15 (2H, d, J=8.8 Hz), 7.31-7.37 (1H, m), 7.40-7.57 (4H, m), 8.77 (1H, d, J=9.1 Hz);

MASS (ES+): m/e 354.20 (M+1).

The compounds obtained by the above-mentioned Preparations and Examples are listed in the following Table 2 (including Tables 2-1 to 2-13) and Table 3 (including Tables 3-1 and 3-2).

Table 2

Table 2-1

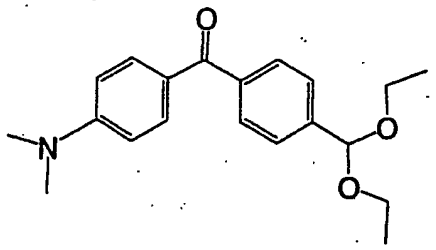
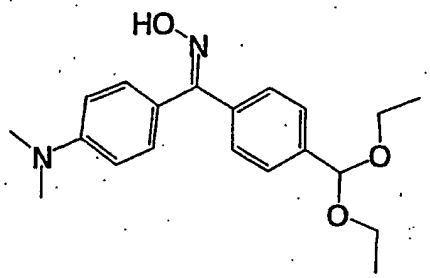
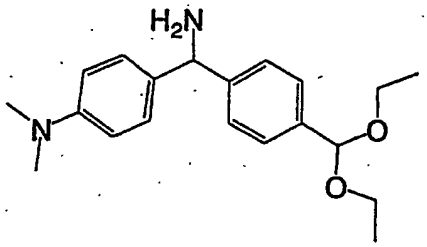
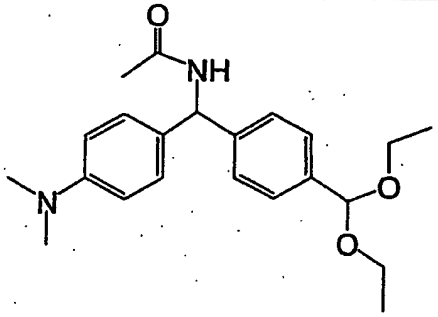
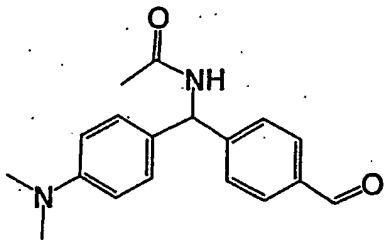
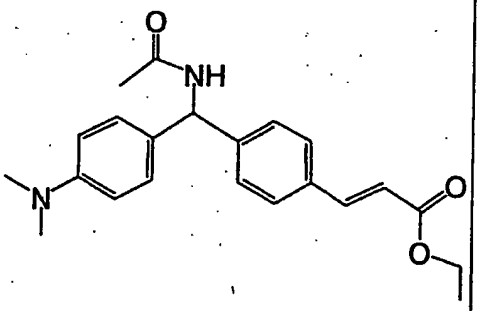
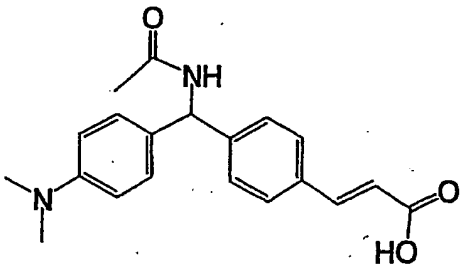
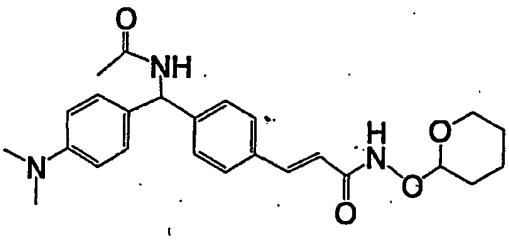
Compound (1)	Compound (2)
	
Compound (3)	**Compound (4)**
	
Compound (5)	**Compound (6)**
	
Compound (7)	**Compound (8)**
	

Table 2-2

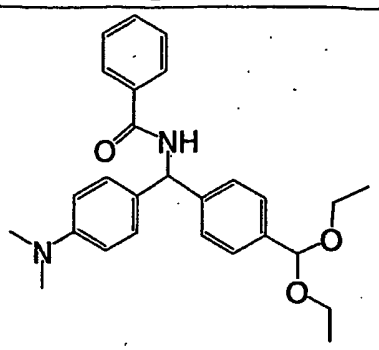
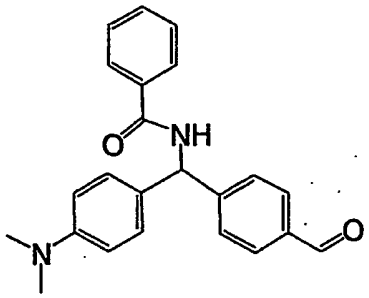
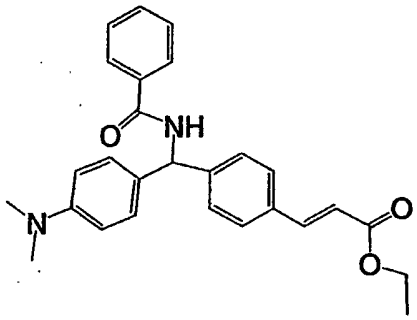
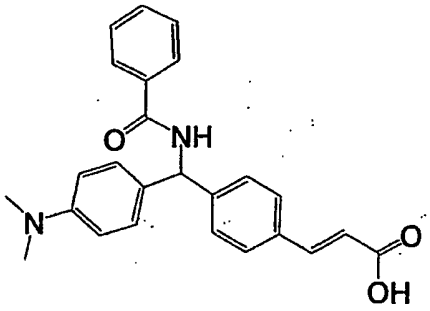
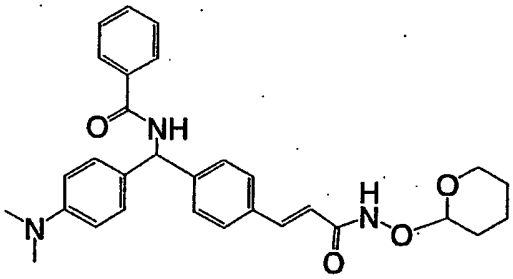
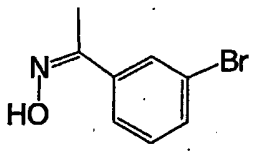
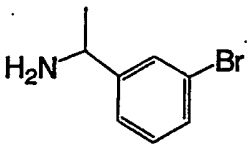
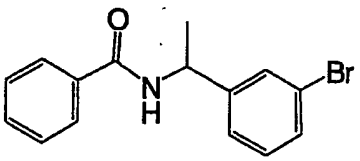
Compound (9)	Compound (10)
	
Compound (11)	**Compound (12)**
	
Compound (13)	**Compound (14)**
	
Compound (15)	**Compound (16)**
	

Table 2-3

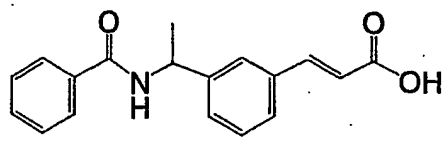
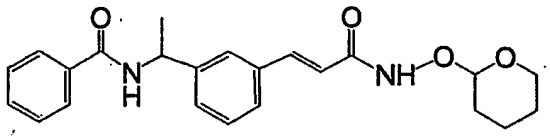
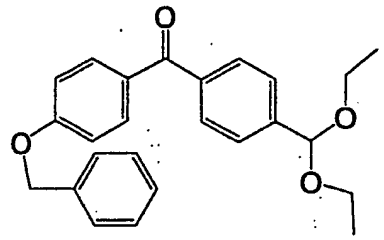
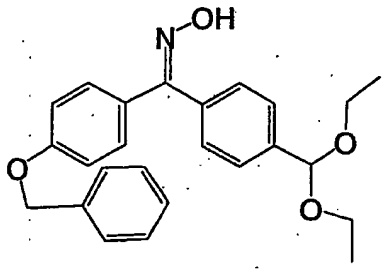
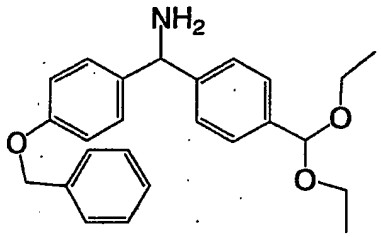
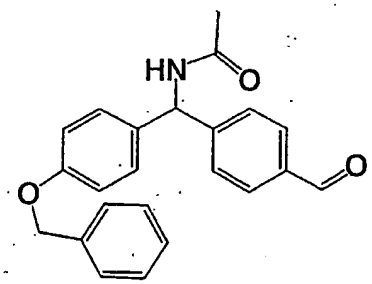
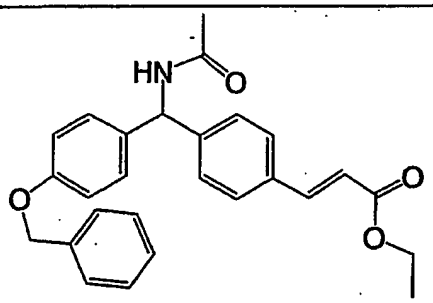
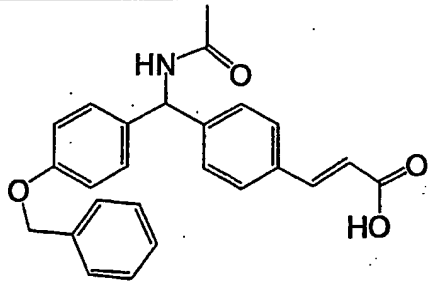
Compound (17)	Compound (18)
	
Compound (19)	**Compound (20)**
	
Compound (21)	**Compound (22)**
	
Compound (23)	**Compound (24)**
	

Table 2-4

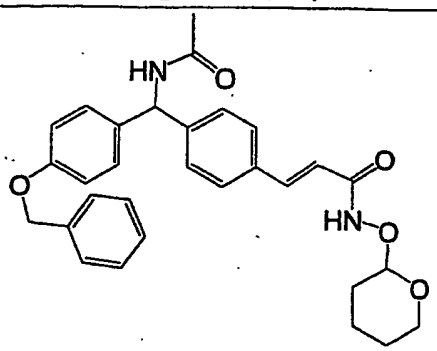
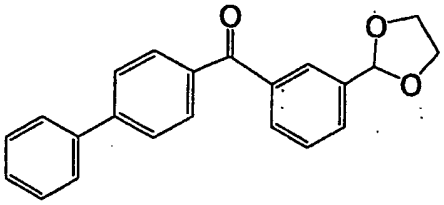
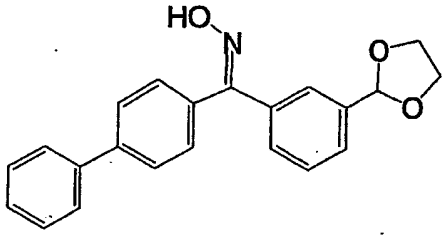
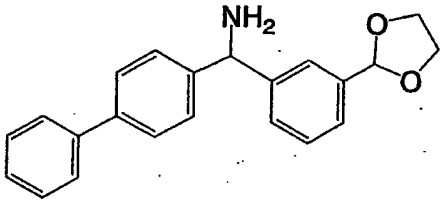
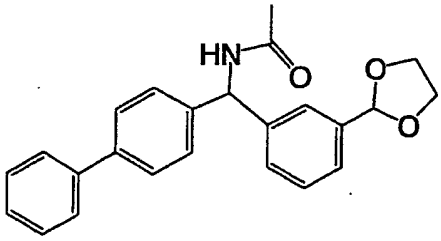
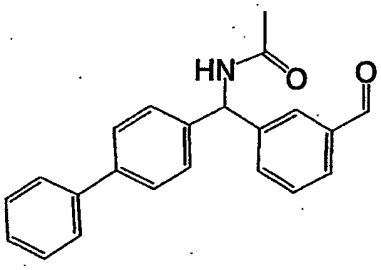
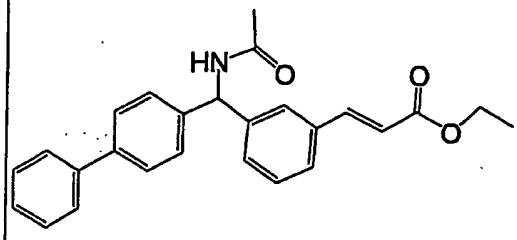
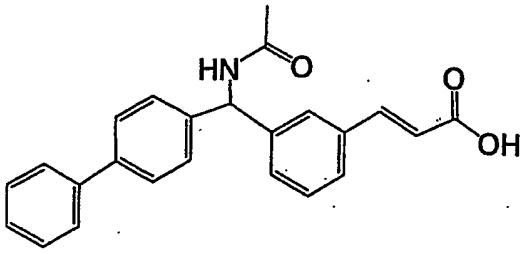
Compound (25)	Compound (26)
	
Compound (27)	**Compound (28)**
	
Compound (29)	**Compound (30)**
	
Compound (31)	**Compound (32)**
	

Table 2-5

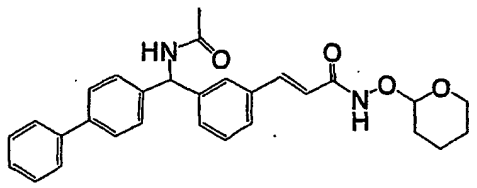
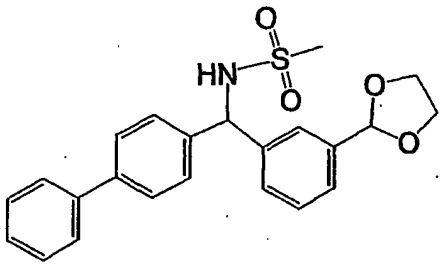
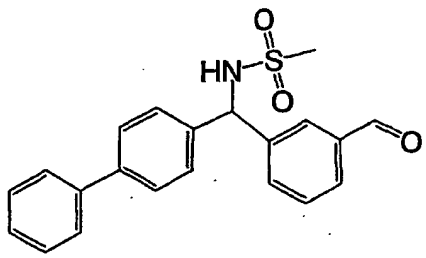
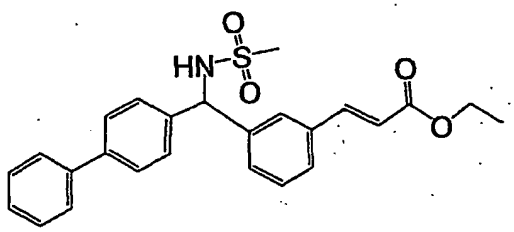
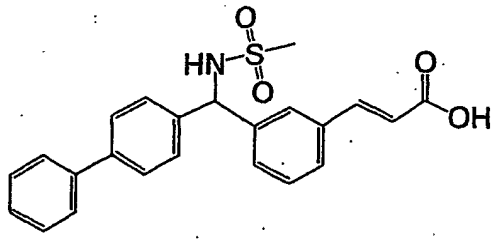
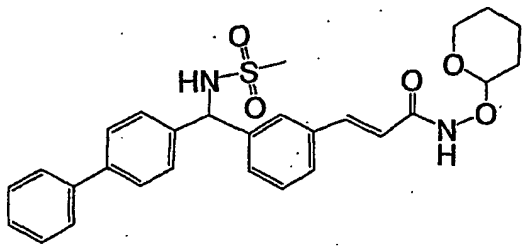
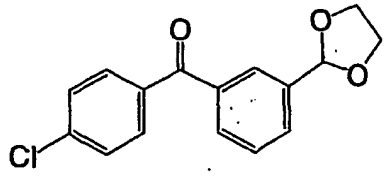
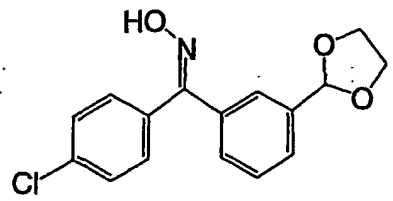
Compound (33)	Compound (34)
	
Compound (35)	**Compound (36)**
	
Compound (37)	**Compound (38)**
	
Compound (39)	**Compound (40)**
	

Table 2-6

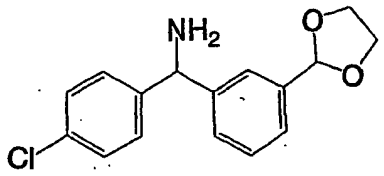
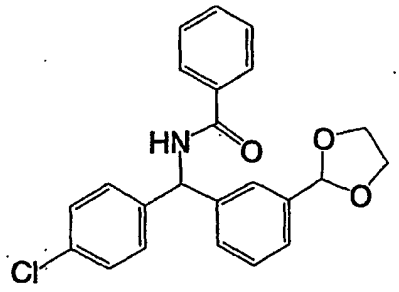
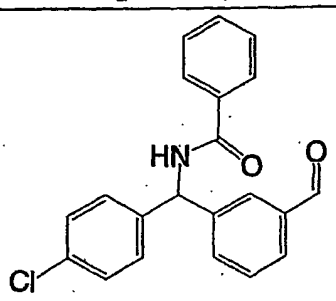
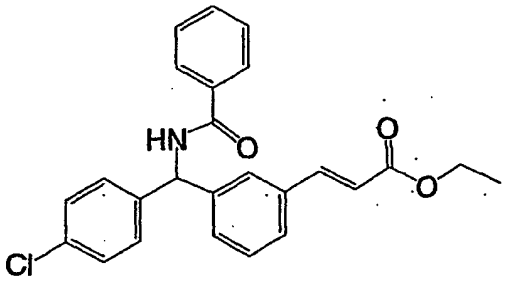
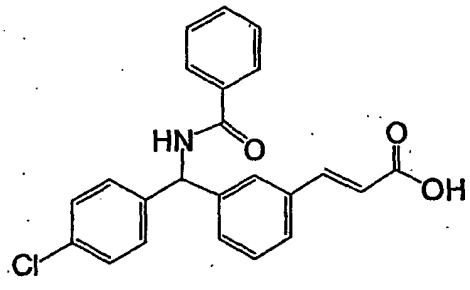
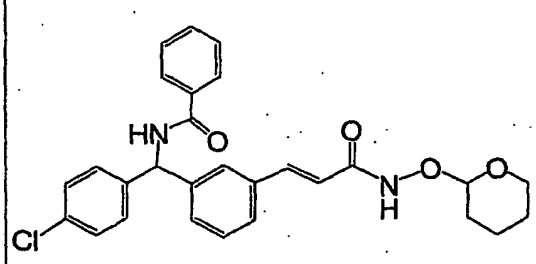
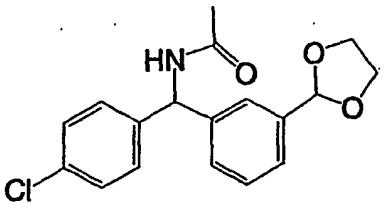
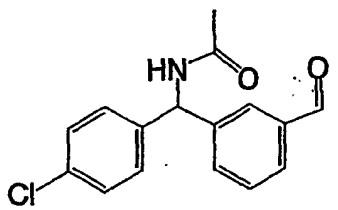
Compound (41)	Compound (42)
	
Compound (43)	**Compound (44)**
	
Compound (45)	**Compound (46)**
	
Compound (47)	**Compound (48)**
	

Table 2-7

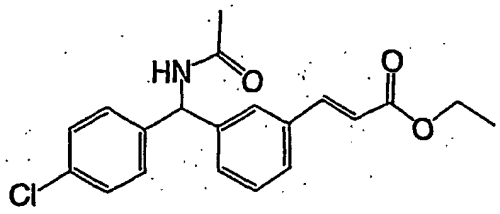
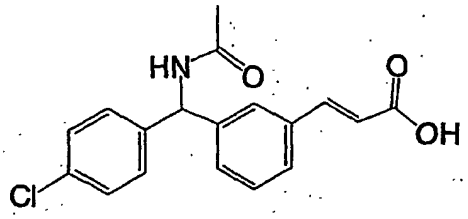
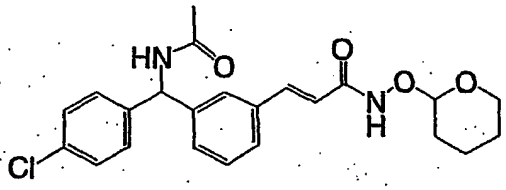
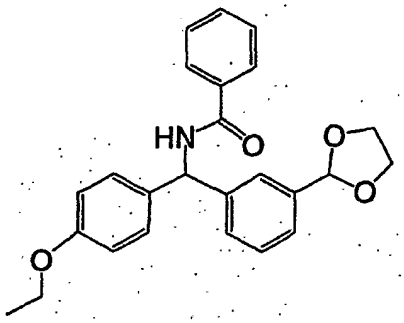
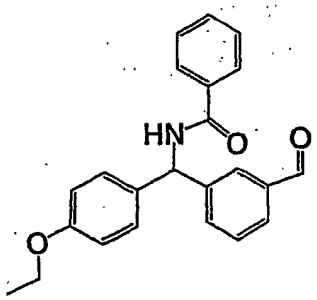
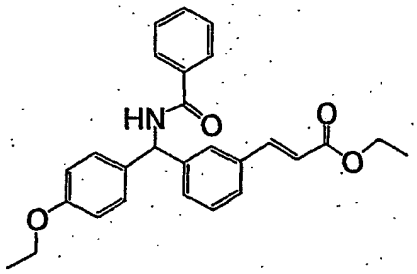
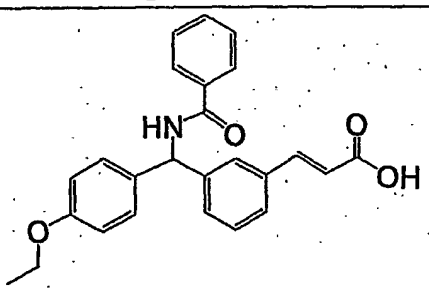
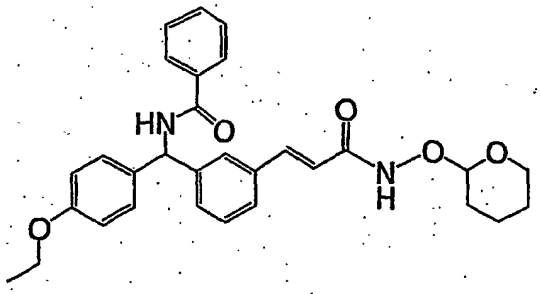
Compound (49)	Compound (50)
	
Compound (51)	**Compound (52)**
	
Compound (53)	**Compound (54)**
	
Compound (55)	**Compound (56)**
	

Table 2-8

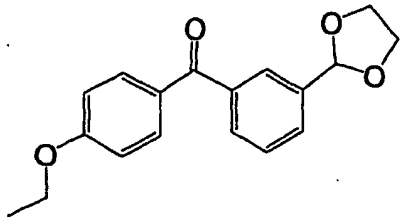
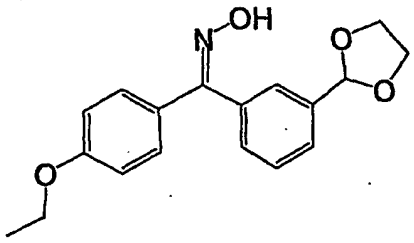
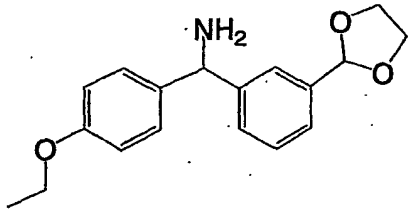
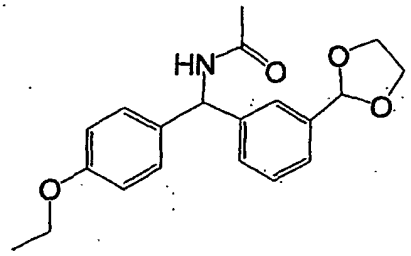
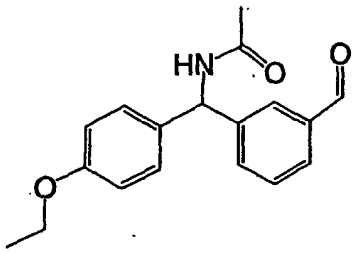
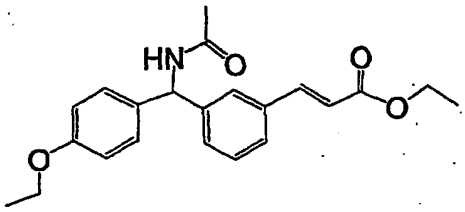
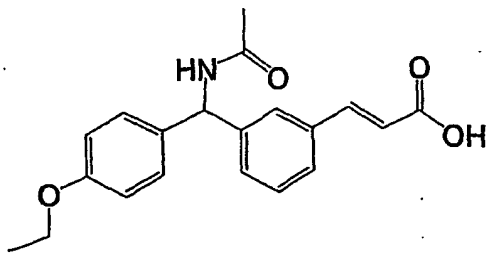
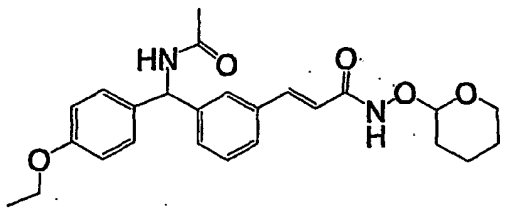
Compound (57)	Compound (58)
	
Compound (59)	**Compound (60)**
	
Compound (61)	**Compound (62)**
	
Compound (63)	**Compound (64)**
	

Table 2-9

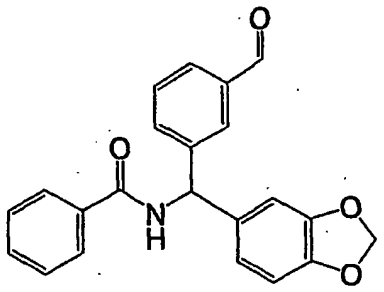
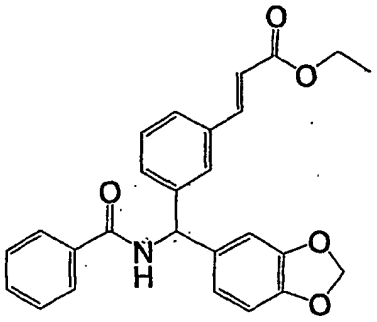
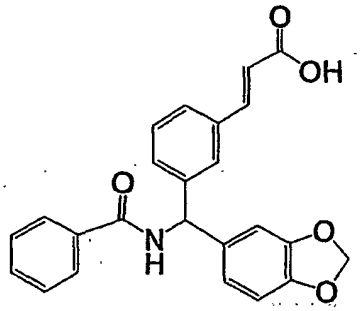
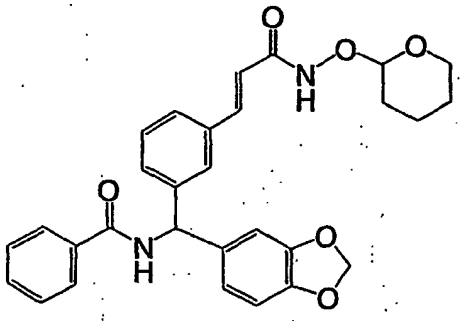
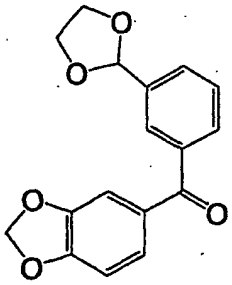
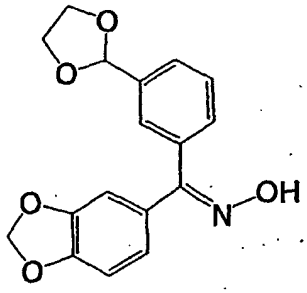
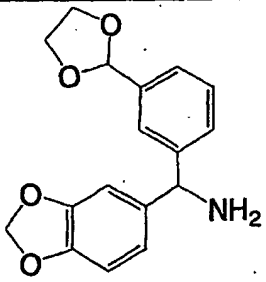
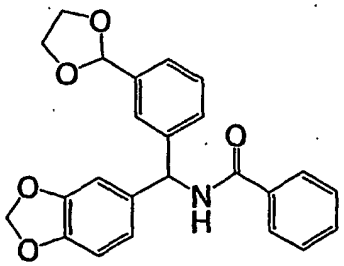
Compound (65)	Compound (66)
	
Compound (67)	**Compound (68)**
	
Compound (69)	**Compound (70)**
	
Compound (71)	**Compound (72)**
	

Table 2-10

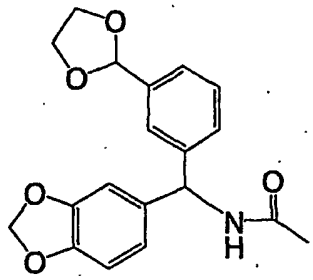
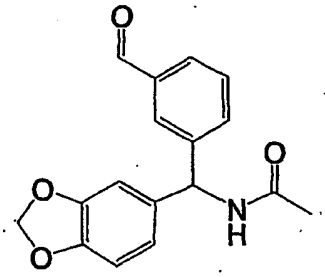
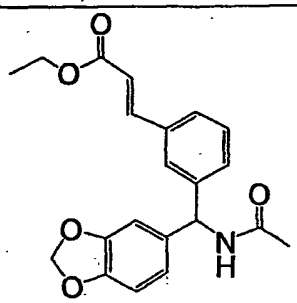
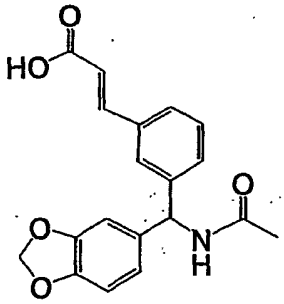
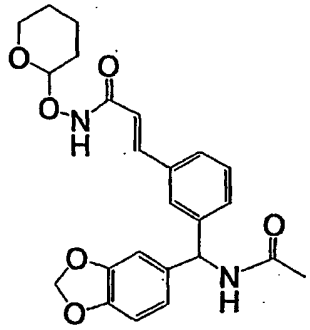
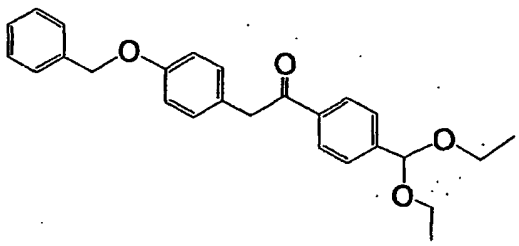
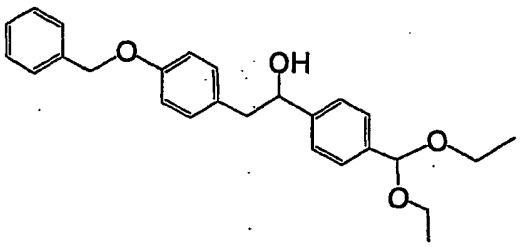
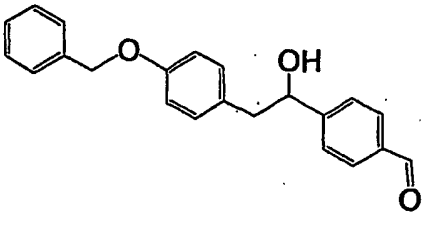
Compound (73)	Compound (74)
	
Compound (75)	**Compound (76)**
	
Compound (77)	**Compound (78)**
	
Compound (79)	**Compound (80)**
	

Table 2-11

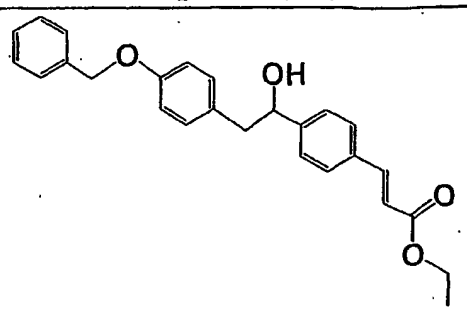
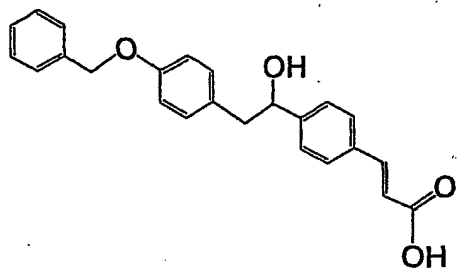
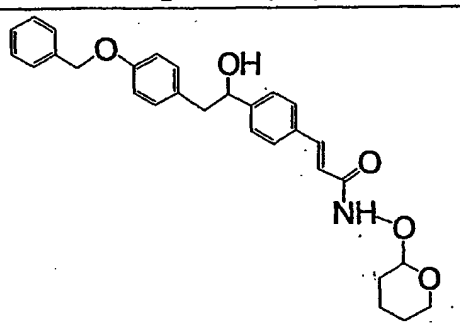
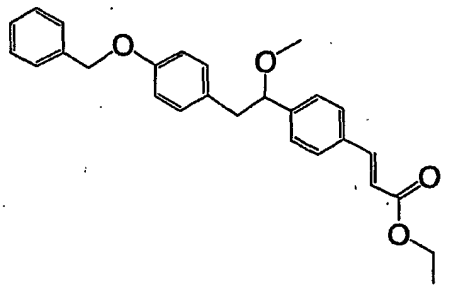
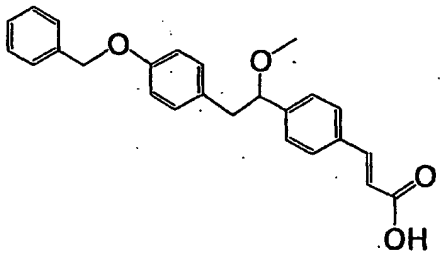
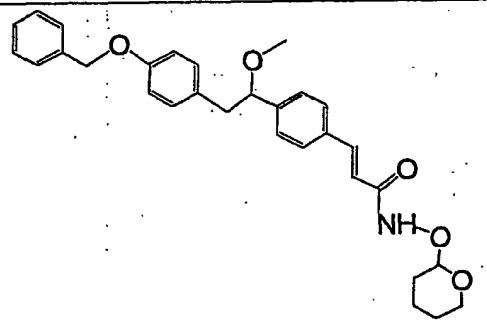
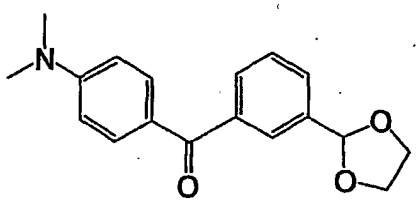
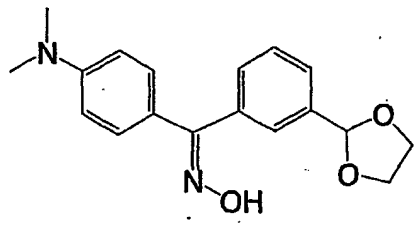
Compound (81)	Compound (82)
	
Compound (83)	**Compound (84)**
	
Compound (85)	**Compound (86)**
	
Compound (87)	**Compound (88)**
	

Table 2-12

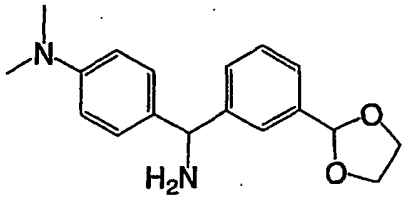
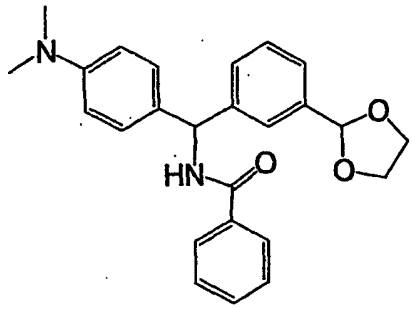
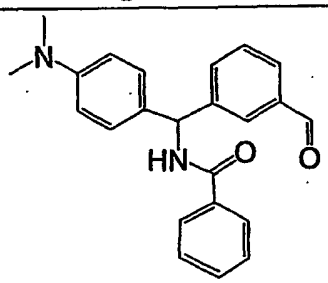
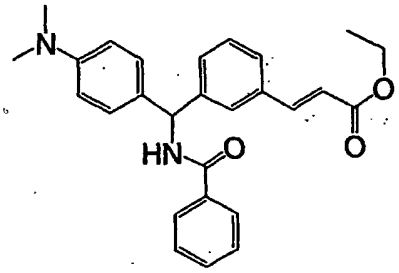
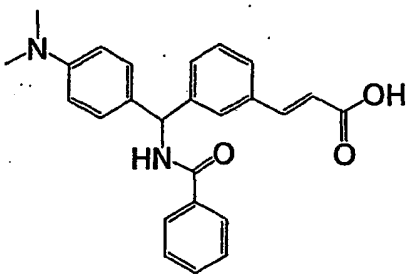
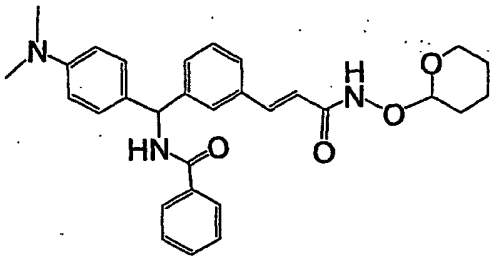
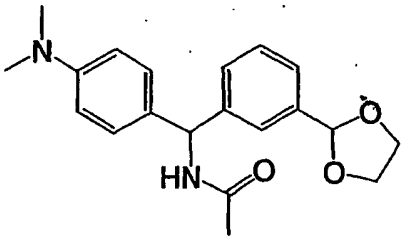
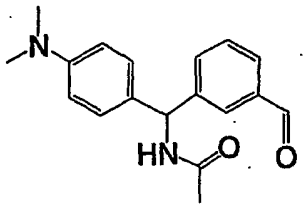
Compound (89)	Compound (90)
	
Compound (91)	**Compound (92)**
	
Compound (93)	**Compound (94)**
	
Compound (95)	**Compound (96)**
	

Table 2-13

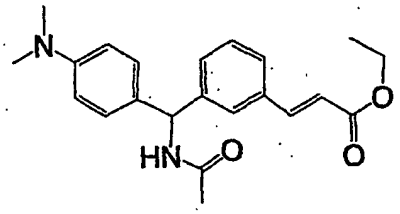
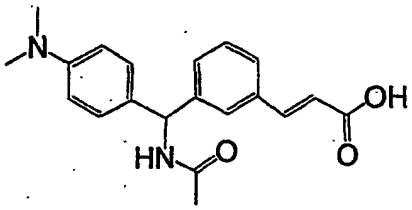
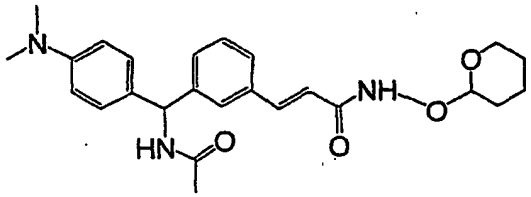
Compound (97)	Compound (98)
	
Compound (99)	
	

Table 3

Table 3-1

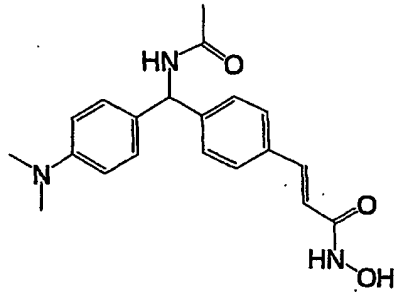
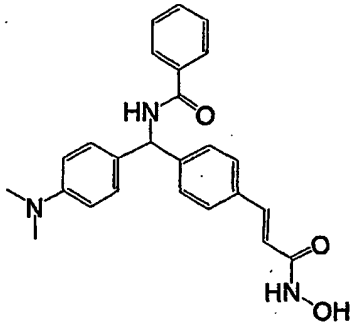
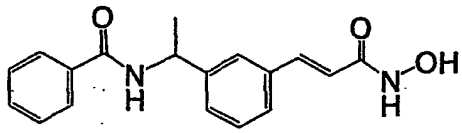
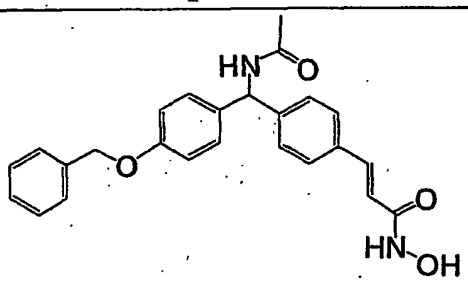
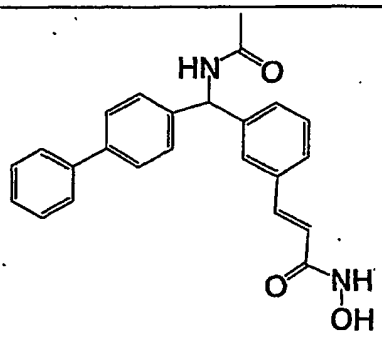
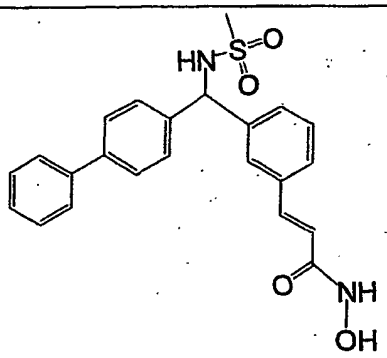
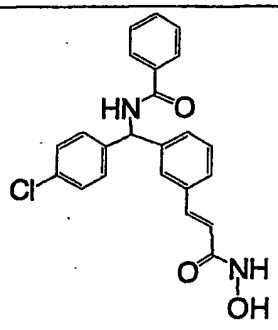
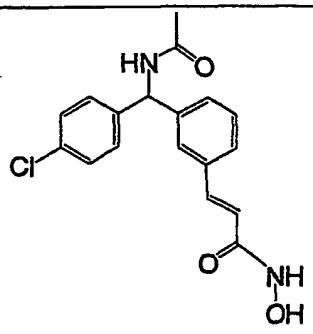
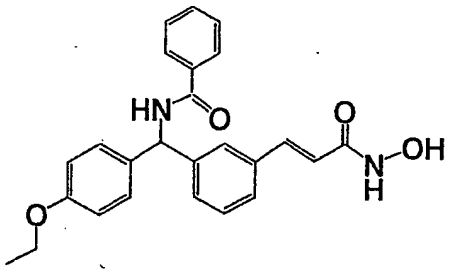
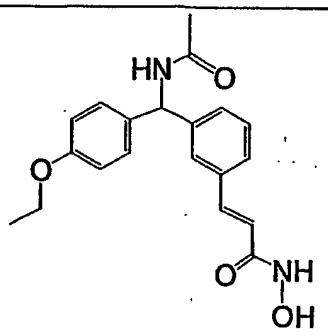
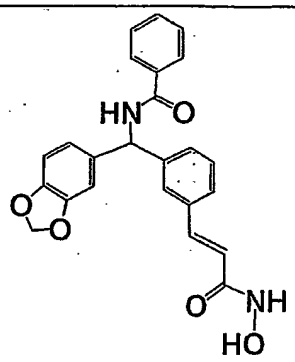
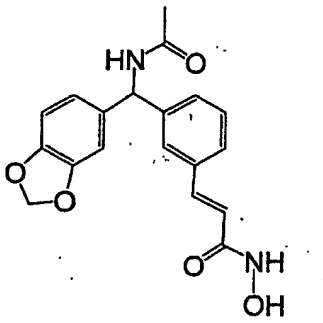
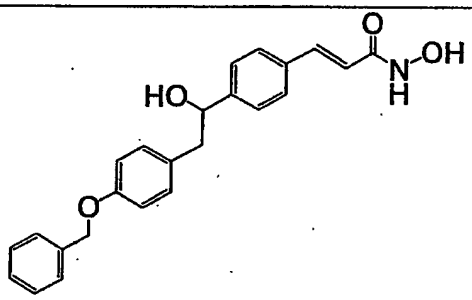
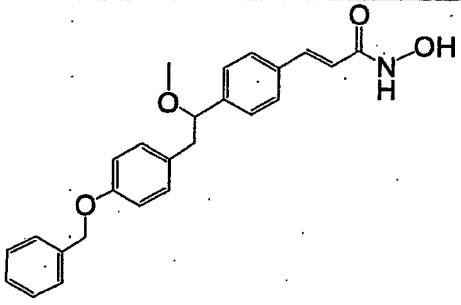
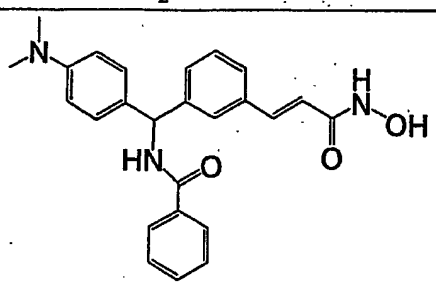
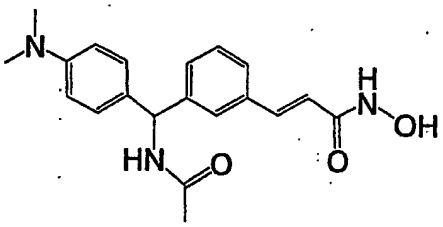
Compound E1	Compound E2
	
Compound E3	**Compound E4**
	
Compound E5	**Compound E6**
	
Compound E7	**Compound E8**
	

Table 3-2

Compound E9	Compound E10
	
Compound E11	**Compound E12**
	
Compound E13	**Compound E14**
	
Compound E15	**Compound E16**
	

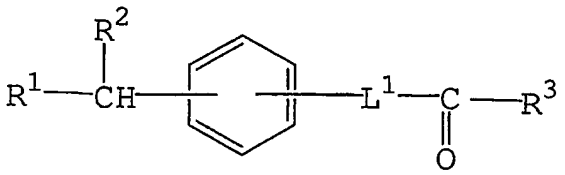
INDUSTRIAL APPLICABILITY

According to the invention, a compound having a potent inhibitory effect on the activity of histone deacetylase and a pharmaceutical composition containing said compound as an active ingredient can be provided. The compound is useful as an active ingredient of an immunosuppressant and an antitumor agent, and useful as a therapeutic or prophylactic agent for diseases such as inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections, tumors, etc.

This application is based on the patent application No. 2003900587 filed in Australia, and the contents of which are incorporated hereinto by reference.

CLAIMS

1. A compound having the following formula (I):



(I)

wherein

R^1 is lower alkyl optionally substituted with one or more suitable substituent(s);
aryl optionally substituted with one or more suitable substituent(s); or
fused ring,

R^2 is acylamino or optionally protected hydroxy,

L^1 is lower alkenylene, and

R^3 is hydroxyamino,

or a salt thereof.

2. The compound of claim 1, wherein

R^1 is lower alkyl optionally substituted with
aryl(lower)alkoxyaryl;
aryl optionally substituted with the group(s) selected from lower alkoxy, halogen, aryl, aryl(lower)alkoxy and mono- or di-substituted amino; or
fused ring, and

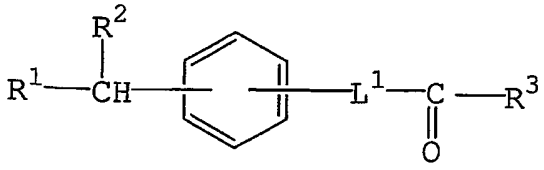
R^2 is acylamino selected from lower alkylcarbonylamino, lower alkylsulfonylamino and arylcarbonylamino; or
hydroxy optionally protected with lower alkyl,

or a salt thereof.

3. A pharmaceutical composition containing the compound of claim 1 or 2 as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

4. The compound of claim 1 or 2 for use as a medicament.

5. A histone deacetylase inhibitor comprising a compound having the following formula (I):



(I)

wherein

R^1 is lower alkyl optionally substituted with one or more suitable substituent(s);
aryl optionally substituted with one or more suitable substituent(s); or
fused ring,

R^2 is acylamino or optionally protected hydroxy,

L^1 is lower alkenylene, and

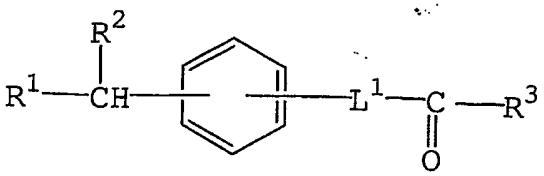
R^3 is hydroxyamino,

or a salt thereof.

6. A method for inhibiting histone deacetylase, comprising using the compound (I) of claim 5.

7. Use of the compound (I) of claim 5 for the manufacture of a medicament for inhibiting histone deacetylase.

8. A pharmaceutical composition for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors, which comprises a compound of the following formula (I) as an active ingredient:



(I)

wherein

R^1 is lower alkyl optionally substituted with one or more suitable substituent(s); aryl optionally substituted with one or more suitable substituent(s); or fused ring,

R^2 is acylamino or optionally protected hydroxy,

L^1 is lower alkenylene, and

R^3 is hydroxyamino,

or a salt thereof.

9. A method for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors, which comprises administering an effective amount of the compound (I) of claim 1 to a human being or an animal.

10. Use of the compound (I) of claim 1 for the manufacture of a medicament for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors.

11. A commercial package comprising the pharmaceutical composition of claim 8 and a written matter associated therewith, the written matter stating that the pharmaceutical composition may or should be used for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors.